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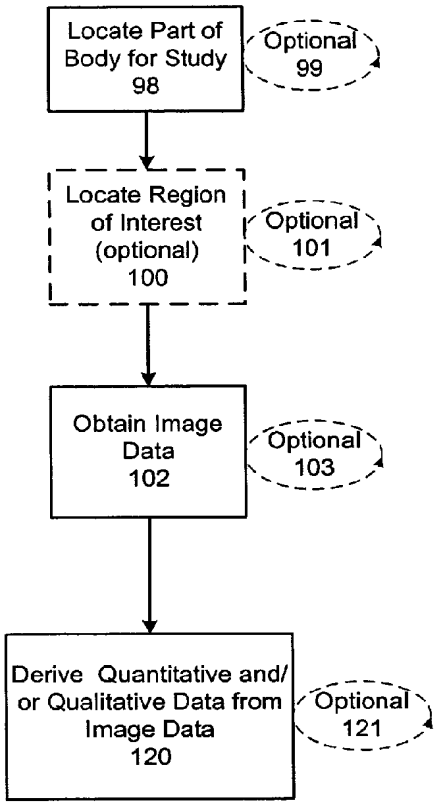
(54) Title: IMAGING MARKERS IN MUSCULOSKELETAL DISEASE



(57) Abstract: This invention is directed to methods for using imaging methods to aid in drug discovery, and drug development. This invention also relates to methods of using imaging methods for diagnosis, prognostication, monitoring and patient management of musculoskeletal disease.

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IMAGING MARKERS IN MUSCULOSKELETAL DISEASE

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TECHNICAL FIELD

[001] This invention relates to using imaging methods to aid in drug discovery and drug development. This invention also relates to using imaging methods for diagnosis, prognostication, monitoring and management of disease, particularly where that disease affects the musculoskeletal system. This invention identifies novel imaging markers for use in diagnosis, prognostication, monitoring and management of disease, including musculoskeletal disease.

BACKGROUND

[002] Osteoporosis and osteoarthritis are among the most common conditions to affect the musculoskeletal system, as well as frequent causes of locomotor pain and disability. Osteoporosis can occur in both human and animal subjects (e.g. horses). Osteoporosis (OP) and osteoarthritis (OA) occur in a substantial portion of the human population over the age of fifty. The National Osteoporosis Foundation (www.nof.org) estimates that as many as 44 million Americans are affected by osteoporosis and low bone mass. In 1997 the estimated cost for osteoporosis related fractures was $13 billion. That figure increased to $17 billion in 2002 and is projected to increase to $210-240 billion by 2040. Currently it is expected that one in two women over the age of 50 will suffer an osteoporosis-related fracture.

[003] In spite of its societal impact and prevalence, there is a paucity of information on the factors that cause osteoporosis and osteoarthritis to progress more rapidly in some individuals than others. Previously considered diseases with little opportunity for therapeutic intervention, osteoporosis and osteoarthritis are now increasingly viewed as a dynamic process with potential for new pharmacologic and surgical treatment modalities.

[004] However, the appropriate deployment and selection of treatment interventions for OP and OA is dependent on the development of better methods for the assessment of the condition of a patient. Moreover, better methods for the assessment of the condition of a patient can also help with drug discovery, drug development, diagnosis, prognostication, disease monitoring, therapeutic monitoring and patient management.

[005] The present invention discloses novel methods and techniques for assessing the condition of a bone(s) and/or a joint(s).

SUMMARY OF THE INVENTION

[006] The invention discloses a method for analyzing at least one of bone mineral density, bone structure and surrounding tissue. The method typically comprises: (a)obtaining an image of a subject; (b) locating a region of interest on the image; (c) obtaining data from the region of interest; and (d) deriving data selected from the group of qualitative and quantitative from the image data obtained at step c.

[007] Further, a kit is provided for aiding in the assessment of the condition of at least one of a bone and joint. The kit typically comprises a software program which reads at least one of a degeneration pattern, a pattern of normal tissue, a pattern of abnormal tissue, and a pattern of diseased tissue. The kit can also include a database of measurements for comparison to the at least one of degeneration pattern, pattern of normal tissue, pattern of abnormal tissue, and pattern of diseased tissue. Additionally, the kit can include a subset of a database of measurements for comparison to the at least one of degeneration pattern, pattern of normal tissue, pattern of abnormal tissue, and pattern of diseased tissue.

[008] The invention also includes at least one of an automated and semi-automated method of using an imaging marker. This automatic or semi-automatic method comprises: obtaining image data from a subject; obtaining data from the image data wherein the data obtained is at least one of quantitative and qualitative data; and administering an agent. Either the automated or semi-automated method can be used for: drug discovery, diagnosis, disease staging, disease monitoring, disease management, prognostication, therapy monitoring, drug efficacy monitoring, and disease prediction.

[009] In another embodiment, a system for monitoring the efficacy of an agent and/or a system for drug discovery is provided. The system includes: administering an agent to a subject; obtaining image data; and obtaining data from the image data wherein the data obtained is at least one of quantitative and qualitative data.

[010] A system is also provided for diagnosing a disease, determining disease staging, monitoring disease progression, managing a disease, disease prognostication, predicting a disease, monitoring therapy and/or randomizing a subject within a group of patients comprising. Any of these systems can include the steps of: (a) obtaining image data of a subject; (b) obtaining data from the image data wherein the data obtained is at least one of quantitative and qualitative data; and (c) comparing the at least one of quantitative and qualitative data in step b to at least one of: a database of at least one of quantitative and qualitative data obtained from a group of subjects; at least one of quantitative and qualitative data obtained from the subject; and at least one of a quantitative and qualitative data obtained from the subject at time Tn.

[011] In any of these described invention, additional steps can be provided. Such additional steps include, for example, enhancing image data.

[012] Suitable subjects for these steps include for example mammals, humans and horses. Suitable anatomical regions of subjects include, for example, dental, spine, hip, knee and bone core x-rays.

[013] A variety of systems can be employed to practice the inventions. Typically at least one of the steps of any of the methods is performed on a first computer. Although, it is possible to have an arrangement where at least one of the steps of the method is performed on a first computer and at least one of the steps of the method is performed on a second computer. In this scenario the first computer and the second computer are typically connected. Suitable connections include, for example, a peer to peer network, direct link, intranet, and internet.

[014] It is important to note that any or all of the steps of the inventions disclosed can be repeated one or more times in series or in parallel with or without the repetition of other steps in the various methods. This includes, for example repeating the step of locating a region of interest, or obtaining image data.

[015] Data can also be converted from 2D to 3D to 4D and back; or from 2D to 4D. Data conversion can occur at multiple points of processing the information. For example, data conversion can occur before or after pattern evaluation and/or analysis.

[016] Any of the processes described herein are suitable for including the step of administering a candidate agent, where that step has not already been performed. Suitable agents include, for example, substances administered to a subject, substances ingested by a subject, molecules, pharmaceuticals, biopharmaceuticals, agropharmaceuticals, genetically manufactured and altered substances, etc.

[017] Any data obtained, extracted or generated under any of the methods can be compared to a database, a subset of a database, or data previously obtained, extracted or generated from the subject.

[018] The present invention provides methods that allow for the analysis of bone mineral density, bone and/or cartilage structure and morphology and/or surrounding tissue from images including electronic images and, accordingly, allows for the evaluation of the effect(s) of an agent (or agents) on bone and/or cartilage. It is important to note that an effect on bone and/or cartilage can occur in agents intended to have an effect, such as a therapeutic effect, on bone and/or cartilage as well as agents intended to primarily effect other tissues in the body but which have a secondary, or tangential, effect on bone and/or cartilage. The images (*e.g.,* x-ray images) can be, for example, dental, hip, spine or other radiographs and can be taken from any mammal. The images can be in electronic format.

[019] The invention includes a method to derive quantitative information on bone structure and/or bone mineral density from an image comprising (a) obtaining an image, wherein the image optionally includes an external standard for determining bone density and/or structure; and (b) analyzing the image obtained in step (a) to derive quantitative information on bone structure. The image is taken of a region of interest (ROI). Suitable ROI include, for example, a hip radiograph or a dental x-ray obtained on dental x-ray film, including the mandible, maxilla or one or more teeth. In certain embodiments, the image is obtained digitally, for example using a selenium detector system, a silicon detector system or a computed radiography system. In other embodiments, the image can be digitized from film, or another suitable source, for analysis.

[020] A method is included where one or more candidate agents can be tested for its effects on bone. Again, the effect can be a primary effect or a secondary effect. For example, the candidate agent can be administered to a subject; thereafter an electronic image of a portion of a bone of the subject can be obtained; and finally the image obtained can be analyzed for information on bone structure. Information on bone structure can relate to a variety of parameters, including the parameters shown in Table 1, Table 2 and Table 3, infra. The images or data can then be compared to a database of images or data (*e.g.,* "normal" images or data) and/or compared to one or more images or data taken from the same subject prior to administration of the candidate agent or to one or more images or data obtained in a reference population. The candidate agent can, for example, be molecules, proteins, peptides, naturally occurring substances, chemically synthesized

substances, or combinations and cocktails thereof. Typically, an agent is one or more drugs. Further, the agent can be evaluated for the ability to effect bone diseases such as the risk of bone fracture (*e.g.,* osteoporotic fracture).

[021] In any of the methods described herein, the analysis can comprise using one or more computer programs (or units). Additionally, the analysis can comprise identifying one or more regions of interest (ROI) in the image, either prior to, concurrently or after analyzing the image, *e.g.* for information on bone mineral density and/or bone structure. The bone density information can be, for example, areas of highest, lowest or median density. Bone structural information can be, for example, one or more of the parameters shown in Table 1, Table 2 and Table 3. The various analyses can be performed concurrently or in series. Further, when using two or more indices each of the indices can be weighted equally or differently, or combinations thereof where more than two indices are employed. Additionally, any of these methods can also include analyzing the image for bone mineral density information using any of the methods described herein.

[022] Any of the methods described herein can further comprise applying one or more correction factors to the data obtained from the image. For example, correction factors can be programmed into a computer unit. The computer unit can be the same one that performs the analysis of the image or can be a different unit. In certain embodiments, the correction factors account for the variation in soft-tissue thickness in individual subjects.

[023] These and other embodiments of the subject invention will readily occur to those of skill in the art in light of the disclosure herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[024] **FIGS. 1A AND B** are block diagrams showing the steps for extracting data from an image and then deriving quantitative and/or qualitative data from the image.

[025] **FIGS. 2A-C** are diagrams showing an image taken of a region of anatomical interest further illustrating possible locations of regions of interest for analysis.

[026] **FIGS. 3A-J** illustrate various abnormalities that might occur including, for example, cartilage defects, bone marrow edema, subchondral sclerosis, osteophytes and cysts.

[027] FIGS. 4A AND B are block diagrams of the method of FIG. 1A showing that the steps can be repeated.

[028] FIGS. 5A-E are block diagrams illustrating steps involved in evaluating patterns in an image of a region of interest.

[029] FIG. 6A-E are block diagrams illustrating steps involved in deriving quantitative and qualitative data from an image in conjunction with administering candidate molecules or drugs for evaluation.

[030] FIGS. 7A-D are block diagrams illustrating steps involved in comparing derived quantitative and qualitative information to a database or to information obtained at a previous time.

[031] FIGS. 8A-D are block diagrams illustrating steps involved in comparing converting an image to a pattern of normal and diseased tissue

[032] FIG. 9 is a diagram showing the use one or more devices in the process of developing a degeneration pattern and using a database for degeneration patterns.

DETAILED DESCRIPTION

[033] The following description is presented to enable any person skilled in the art to make and use the invention. Various modifications to the embodiments described will be readily apparent to those skilled in the art, and the generic principles defined herein can be applied to other embodiments and applications without departing from the spirit and scope of the present invention as defined by the appended claims. Thus, the present invention is not intended to be limited to the embodiments shown, but is to be accorded the widest scope consistent with the principles and features disclosed herein. To the extent necessary to achieve a complete understanding of the invention disclosed, the specification and drawings of all issued patents, patent publications, and patent applications cited in this application are incorporated herein by reference.

[034] The practice of the present invention employs, unless otherwise indicated, currently conventional methods of imaging and image processing within the skill of the art. Such techniques are explained fully in the literature. See, e.g., WO 02/22014, X-Ray Structure Determination: A Practical Guide, 2nd Edition, editors Stout and Jensen, 1989, John Wiley & Sons, publisher; Body CT: A Practical Approach, editor Slone, 1999, McGraw-Hill publisher; The Essential Physics of Medical Imaging, editors Bushberg, Seibert, Leidholdt Jr & Boone, 2002, Lippincott, Williams & Wilkins; X-ray Diagnosis: A

Physician's Approach, editor Lam, 1998 Springer-Verlag, publisher; Dental Radiology: Understanding the X-Ray Image, editor Laetitia Brocklebank 1997, Oxford University Press publisher; and Digital Image Processing, editor Kenneth R. Castleman, 1996 Prentice Hall, publisher; The Image Processing Handbook, editor John C. Russ, 3rd Edition, 1998, CRC Press; Active Contours: The Application of Techniques from Graphics, Vision, Control Theory and Statistics to Visual Tracking of Shapes in Motion, Editors Andrew Blake, Michael Isard, 1999 Springer Verlag. As will be appreciated by those of skill in the art, as the field of imaging continues to advance methods of imaging currently employed can evolve over time. Thus, any imaging method or technique that is currently employed is appropriate for application of the teachings of this invention as well as techniques that can be developed in the future. A further detailed description of imaging methods is not provided in order to avoid obscuring the invention.

[035] As shown in **FIG. 1A**, the first step is to locate a part of the body of a subject, for example in a human body, for study ***98.*** The part of the body located for study is the region of anatomical interest (RAI). In locating a part of the body for study, a determination is made to, for example, take an image or a series of images of the body at a particular location, e.g. hip, dental, spine, etc. Images include, for example, conventional x-ray images, x-ray tomosynthesis, ultrasound (including A-scan, B-scan and C-scan) computed tomography (CT scan), magnetic resonance imaging (MRI), optical coherence tomography, single photon emission tomography (SPECT), and positron emission tomography, or such other imaging tools that a person of skill in the art would find useful in practicing the invention. Once the image is taken, a region of interest (ROI) can be located within the image ***100***. Image data is extracted from the image ***102***. Finally, quantitative and/or qualitative data is extracted from the image data ***120***. The quantitative and/or qualitative data extracted from the image includes, for example, the parameters and measurements shown in Table 1, Table 2 or Table 3.

[036] Each step of locating a part of the body for study ***98,*** optionally locating a region of interest ***100,*** obtaining image data ***102***, and deriving data ***120***, can be repeated one or more times ***99,101, 103, 121***, respectively, as desired.

[037] As shown in **FIG. 1B** image data can be optionally enhanced ***104*** by applying image processing techniques, such as noise filtering or diffusion filtering, to facilitate further analysis. Similar to the process shown in **FIG. 1A**, locating a part of the body for study ***98,*** optionally locating a region of interest ***100,*** obtaining image data ***102***, enhancing

image data ***104,*** and deriving data ***120***, can be repeated one or more times ***99,101, 103, 105, 121***, respectively, as desired.

TABLE 1
Representative Parameters Measured with Quantitative and Qualitative Image Analysis Methods

PARAMETER	MEASUREMENTS
Bone parameters	• Stainless steel equivalent thickness (Average gray value of the region of interest expressed as thickness of stainless steel with equivalent intensity) • Trabecular contrast • (Trabecular equivalent thickness / Marrow equivalent thickness) • Fractal dimension • Fourier spectral analysis (Mean transform coefficient absolute value and mean spatial first moment) • Predominant orientation of spatial energy spectrum • Trabecular area (Pixel count of extracted trabeculae) • Trabecular area / Total area • Trabecular perimeter (Count of trabecular pixels with marrow pixels in their neighborhood, proximity or vicinity) • Trabecular distance transform (For each trabecular pixel, calculation of distance to closest marrow pixel) • Marrow distance transform (For each marrow pixel, calculation of distance to closest trabecular pixel) • Trabecular distance transform regional maximal values (mean, min., max, std. Dev). (Describes thickness and thickness variation of trabeculae) • Marrow distance transform regional maximal values (mean, min., max, std. Dev) • Star volume (Mean volume of all the parts of an object which can be seen unobscured from a random point inside the object in all possible directions) • Trabecular Bone Pattern Factor (TBPf = (P1 - P2) / (A1 - A2) where P1 and A1 are the perimeter length and trabecular bone area before dilation and P2 and A2 corresponding values after a single pixel dilation, measure of connectivity) • Connected skeleton count or Trees (T) • Node count (N) • Segment count (S) • Node-to-node segment count (NN) • Node-to-free-end segment count (NF) • Node-to-node segment length (NNL) • Node-to-free-end segment length (NFL) • Free-end-to-free-end segment length (FFL) • Node-to-node total struts length (NN.TSL) • Free-end-to-free-ends total struts length(FF.TSL) • Total struts length (TSL) • FF.TSL/ TSL • NN.TSL/ TSL

PARAMETER	MEASUREMENTS
	• Loop count (Lo) • Loop area • Mean distance transform values for each connected skeleton • Mean distance transform values for each segment (Tb.Th) • Mean distance transform values for each node-to-node segment (Tb.Th.NN) • Mean distance transform values for each node-to-free-end segment (Tb.Th.NF) • Orientation (angle) of each segment • Angle between segments • Length-thickness ratios (NNL/Tb.Th.NN) and (NFL/ Tb.Th.NF) • Interconnectivity index (ICI) ICI = (N * NN)/ (T * (NF + 1))
Cartilage and cartilage defect/diseased cartilage parameters	• Total cartilage volume • Partial/Focal cartilage volume • Cartilage thickness distribution (thickness map) • Mean cartilage thickness for total region or focal region • Median cartilage thickness for total region or focal region • Maximum cartilage thickness for total region or focal region • Minimum cartilage thickness for total region or focal region • 3D cartilage surface information for total region or focal region • Cartilage curvature analysis for total region or focal region • Volume of cartilage defect/diseased cartilage • Depth of cartilage defect/diseased cartilage • Area of cartilage defect/diseased cartilage • 2D or 3D location of cartilage defect/diseased cartilage in articular surface • 2D or 3D location of cartilage defect/diseased cartilage in relationship to weight-bearing area • **Ratio: diameter of cartilage defect or diseased cartilage / thickness of surrounding normal cartilage** • **Ratio: depth of cartilage defect or diseased cartilage / thickness of surrounding normal cartilage** • **Ratio: volume of cartilage defect or diseased cartilage / thickness of surrounding normal cartilage** • **Ratio: surface area of cartilage defect or diseased cartilage / total joint or articular surface area** • **Ratio: volume of cartilage defect or diseased cartilage / total cartilage volume**
Other articular parameters	• Presence or absence of bone marrow edema • Volume of bone marrow edema • Volume of bone marrow edema normalized by width, area, size, volume of femoral condyle(s)/tibial plateau/patella – other bones in other joints • Presence or absence of osteophytes • Presence or absence of subchondral cysts • Presence or absence of subchondral sclerosis • Volume of osteophytes • Volume of subchondral cysts • Volume of subchondral sclerosis • Area of bone marrow edema • Area of osteophytes • Area of subchondral cysts • Area of subchondral sclerosis • Depth of bone marrow edema • Depth of osteophytes • Depth of subchondral cysts

PARAMETER	MEASUREMENTS
	• Depth of subchondral sclerosis • Volume, area, depth of osteophytes, subchondral cysts, subchondral sclerosis normalized by width, area, size, volume of femoral condyle(s)/tibial plateau/patella – other bones in other joints • Presence or absence of meniscal tear • Presence or absence of cruciate ligament tear • Presence or absence of collateral ligament tear • Volume of menisci • Ratio of volume of normal to torn/damaged or degenerated meniscal tissue • Ratio of surface area of normal to torn/damaged or degenerated meniscal tissue • Ratio of surface area of normal to torn/damaged or degenerated meniscal tissue to total joint or cartilage surface area • Ratio of surface area of torn/damaged or degenerated meniscal tissue to total joint or cartilage surface area • Size ratio of opposing articular surfaces • Meniscal subluxation/dislocation in mm • Index combining different articular parameters which can also include o Presence or absence of cruciate or collateral ligament tear o Body mass index, weight, height • 3D surface contour information of subchondral bone • Actual or predicted knee flexion angle during gait cycle (latter based on gait patterns from subjects with matching demographic data retrieved from motion profile database) • Predicted knee rotation during gait cycle • Predicted knee displacement during gait cycle • Predicted load bearing line on cartilage surface during gait cycle and measurement of distance between load bearing line and cartilage defect/diseased cartilage • Predicted load bearing area on cartilage surface during gait cycle and measurement of distance between load bearing area and cartilage defect/diseased cartilage • Predicted load bearing line on cartilage surface during standing or different degrees of knee flexion and extension and measurement of distance between load bearing line and cartilage defect/diseased cartilage • Predicted load bearing area on cartilage surface during standing or different degrees of knee flexion and extension and measurement of distance between load bearing area and cartilage defect/diseased cartilage • Ratio of load bearing area to area of cartilage defect/diseased cartilage • Percentage of load bearing area affected by cartilage disease • Location of cartilage defect within load bearing area • Load applied to cartilage defect, area of diseased cartilage • Load applied to cartilage adjacent to cartilage defect, area of diseased cartilage

[038] As will be appreciated by those of skill in the art, the parameters and measurements shown in Table 1 are provided for illustration purposes. Other parameters and measurements, ratios, derived values or indices can be used to extract quantitative and/or qualitative information about the ROI without departing from the scope of the

invention. Additionally, where multiple ROI or multiple derivatives of data are used, the parameter measured can be the same parameter or a different parameter without departing from the scope of the invention. Additionally, data from different ROI's can be combined or compared as desired.

[039] Additional measurements can be performed that are selected based on the anatomical structure to be studied as described below.

[040] Once the data is extracted from the image it can be manipulated to assess the severity of the disease and to determine disease staging (e.g., mild, moderate, severe or a numerical value or index). The information can also be used to monitor progression of the disease and/or the efficacy of any interventional steps that have been taken. Finally, the information can be used to predict the progression of the disease or to randomize patient groups in clinical trials.

[041] **FIG. 2A** illustrates an image ***200*** taken of an RAI, shown as ***202***. As shown in **FIG. 2A**, a single region of interest (ROI) ***210*** has been identified within the image. The ROI ***210*** can take up the entire image ***200***, or nearly the entire image. As shown in **FIG. 2B** more than one ROI can be identified in an image. In this example, a first ROI ***220*** is depicted in one region of the image ***200***, and a second ROI ***222*** is depicted within the image. In this instance, neither of these ROI overlap or abut. As will be appreciated by a person of skill in the art, the number of ROI identified in an image ***200*** is not limited to the two depicted. Turning now to **FIG. 2C** another embodiment showing two ROI for illustration purposes is shown. In this instance, the first ROI ***230*** and the second ROI ***232***, are partially overlapping. As will be appreciated by those of skill in the art, where multiple ROI are used any or all of the ROI can be organized such that it does not overlap, it abuts without overlapping, it overlaps partially, it overlaps completely (for example where a first ROI is located completely within a second identified ROI), and combinations thereof. Further the number of ROI per image ***200*** can range from one (ROI_1) to *n* (ROI_n) where *n* is the number of ROI to be analyzed.

[042] Bone density, microarchitecture, macro-anatomic and/or biomechanical (e.g. derived using finite element modeling) analyses can be applied within a region of predefined size and shape and position. This region of interest can also be referred to as a "window." Processing can be applied repeatedly within the window at different positions of the image. For example, a field of sampling points can be generated and the analysis

performed at these points. The results of the analyses for each parameter can be stored in a matrix space, *e.g.,* where its position corresponds to the position of the sampling point where the analysis occurred, thereby forming a map of the spatial distribution of the parameter (a parameter map). The sampling field can have regular intervals or irregular intervals with varying density across the image. The window can have variable size and shape, for example to account for different patient size or anatomy.

[043] The amount of overlap between the windows can be determined, for example, using the interval or density of the sampling points (and resolution of the parameter maps). Thus, the density of sampling points is set higher in regions where higher resolution is desired and set lower where moderate resolution is sufficient, in order to improve processing efficiency. The size and shape of the window would determine the local specificity of the parameter. Window size is preferably set such that it encloses most of the structure being measured. Oversized windows are generally avoided to help ensure that local specificity is not lost.

[044] The shape of the window can be varied to have the same orientation and/or geometry of the local structure being measured to minimize the amount of structure clipping and to maximize local specificity. Thus, both 2D and/or 3D windows can be used, as well as combinations thereof, depending on the nature of the image and data to be acquired.

[045] In another embodiment, bone density, microarchitecture, macro-anatomic and/or biomechanical (e.g. derived using finite element modeling) analyses can be applied within a region of predefined size and shape and position. The region is generally selected to include most, or all, of the anatomic region under investigation and, preferably, the parameters can be assessed on a pixel-by-pixel basis (*e.g.,* in the case of 2D or 3D images) or a voxel-by-voxel basis in the case of cross-sectional or volumetric images (*e.g.,* 3D images obtained using MR and/or CT). Alternatively, the analysis can be applied to clusters of pixels or voxels wherein the size of the clusters is typically selected to represent a compromise between spatial resolution and processing speed. Each type of analysis can yield a parameter map.

[046] Parameter maps can be based on measurement of one or more parameters in the image or window; however, parameter maps can also be derived using statistical methods. In one embodiment, such statistical comparisons can include comparison of

data to a reference population, e.g. using a z-score or a T-score. Thus, parameter maps can include a display of z-scores or T-scores.

[047] Additional measurements relating to the site to be measured can also be taken. For example, measurements can be directed to dental, spine, hip, knee or bone cores. Examples of suitable site specific measurements are shown in Table 2.

TABLE 2
Site specific measurement of bone parameters

Parameters specific to hip x-rays	• All microarchitecture parameters on structures parallel to stress lines • All microarchitecture parameters on structures perpendicular to stress lines Geometry • Shaft angle • Neck angle • Diameter of femur neck • Hip axis length • Largest cross-section of femur head • Average thickness of cortical within ROI • Standard deviation of cortical thickness within ROI • Maximum thickness of cortical within ROI • Minimum thickness of cortical within ROI Hip joint space width
Parameters specific to spine x-rays	• All microarchitecture parameters on vertical structures • All microarchitecture parameters on horizontal structures Geometry • Superior endplate cortical thickness (anterior, center, posterior) • Inferior endplate cortical thickness (anterior, center, posterior) • Anterior vertebral wall cortical thickness (superior, center, inferior) • Posterior vertebral wall cortical thickness (superior, center, inferior) • Superior aspect of pedicle cortical thickness • inferior aspect of pedicle cortical thickness • Vertebral height (anterior, center, posterior) • Vertebral diameter (superior, center, inferior), • Pedicle thickness (supero-inferior direction). • Maximum vertebral height • Minimum vertebral height • Average vertebral height • Anterior vertebral height • Medial vertebral height • Posterior vertebral height • Maximum inter-vertebral height • Minimum inter-vertebral height • Average inter-vertebral height
Parameters specific to knee x-rays	• Average medial joint space width • Minimum medial joint space width • Maximum medial joint space width • Average lateral joint space width • Minimum lateral joint space width • Maximum lateral joint space width

[048] As will be appreciated by those of skill in the art, measurement and image processing techniques are adaptable to be applicable to both microarchitecture and macro-anatomical structures. Examples of these measurements are shown in Table 3.

TABLE 3
Measurements applicable on Microarchitecture and Macro-anatomical Structures

Average density measurement	• Calibrated density of ROI
Measurements on micro-anatomical structures of dental, spine, hip, knee or bone cores x-rays	The following parameters are derived from the extracted structures: • Calibrated density of extracted structures • Calibrated density of background • Average intensity of extracted structures • Average intensity of background (area other than extracted structures) • Structural contrast (average intensity of extracted structures / average intensity of background) • Calibrated structural contrast (calibrated density extracted structures / calibrated density of background) • Total area of extracted structures • Total area of ROI • Area of extracted structures normalized by total area of ROI • Boundary lengths (perimeter) of extracted normalized by total area of ROI • Number of structures normalized by area of ROI • Trabecular bone pattern factor; measures concavity and convexity of structures • Star volume of extracted structures • Star volume of background • Number of loops normalized by area of ROI
Measurements on Distance transform of extracted structures	The following statistics are measured from the distance transform regional maximum values: • Average regional maximum thickness • Standard deviation of regional maximum thickness • Largest value of regional maximum thickness • Median of regional maximum thickness

Measurements on skeleton of extracted structures	• Average length of networks (units of connected segments) • Maximum length of networks • Average thickness of structure units (average distance transform values along skeleton) • Maximum thickness of structure units (maximum distance transform values along skeleton) • Number of nodes normalized by ROI area • Number of segments normalized by ROI area • Number of free-end segments normalized by ROI area • Number of inner (node-to-node) segments normalized ROI area • Average segment lengths • Average free-end segment lengths • Average inner segment lengths • Average orientation angle of segments • Average orientation angle of inner segments • Segment tortuosity; a measure of straightness • Segment solidity; another measure of straightness • Average thickness of segments (average distance transform values along skeleton segments) • Average thickness of free-end segments • Average thickness of inner segments • Ratio of inner segment lengths to inner segment thickness • Ratio of free-end segment lengths to free-end segment thickness • Interconnectivity index; a function of number of inner segments, free-end segments and number of networks.
Directional skeleton segment measurements	All measurement of skeleton segments can be constrained by one or more desired orientation by measuring only skeleton segments within ranges of angle.
Watershed segmentation	Watershed segmentation is applied to gray level images. Statistics of watershed segments are: • Total area of segments • Number of segments normalized by total area of segments • Average area of segments • Standard deviation of segment area • Smallest segment area • Largest segment area

[049] Calibrated density typically refers to the measurement of intensity values of features in images converted to its actual material density or expressed as the density of a reference material whose density is known. The reference material can be metal, polymer, plastics, bone, cartilage, etc., and can be part of the object being imaged or a calibration phantom placed in the imaging field of view during image acquisition.

[050] Extracted structures typically refer to simplified or amplified representations of features derived from images. An example would be binary images of trabecular patterns generated by background subtraction and thresholding. Another example would be binary images of cortical bone generated by applying an edge filter and thresholding.

The binary images can be superimposed on gray level images to generate gray level patterns of structure of interest.

[051] Distance transform typically refers to an operation applied on binary images where maps representing distances of each 0 pixel to the nearest 1 pixel are generated. Distances can be calculated by the Euclidian magnitude, city-block distance, La Place distance or chessboard distance.

[052] Distance transform of extracted structures typically refer to distance transform operation applied to the binary images of extracted structures, such as those discussed above with respect to calibrated density.

[053] Skeleton of extracted structures typically refer to a binary image of 1 pixel wide patterns, representing the centerline of extracted structures. It is generated by applying a skeletonization or medial transform operation, by mathematical morphology or other methods, on an image of extracted structures.

[054] Skeleton segments typically are derived from skeleton of extracted structures by performing pixel neighborhood analysis on each skeleton pixel. This analysis classifies each skeleton pixel as a node pixel or a skeleton segment pixel. A node pixel has more than 2 pixels in its 8-neighborhood. A skeleton segment is a chain of skeleton segment pixels continuously 8-connected. Two skeleton segments are separated by at least one node pixel.

[055] Watershed segmentation as it is commonly known to a person of skill in the art, typically is applied to gray level images to characterize gray level continuity of a structure of interest. The statistics of dimensions of segments generated by the process are, for example, those listed in Table 3 above. As will be appreciated by those of skill in the art, however, other processes can be used without departing from the scope of the invention.

[056] Turning now to **FIG. 3A**, a cross-section of a cartilage defect is shown ***300***. The cross-hatched zone ***302*** corresponds to an area where there is cartilage loss. **FIG. 3B** is a top view of the cartilage defect shown in **FIG. 3A**.

[057] **FIG. 3C** illustrates the depth of a cartilage defect ***310*** in a first cross-section dimension with a dashed line illustrating a projected location of the original cartilage

surface ***312.*** By comparing these two values a ratio of cartilage defect depth to cartilage defect width can be calculated.

[058] **FIG.3D** illustrated the depth of the cartilage ***320*** along with the width of the cartilage defect ***322.*** These two values can be compared to determine a ratio of cartilage depth to cartilage defect width.

[059] **FIG. 3E** shows the depth of the cartilage defect ***310*** along with the depth of the cartilage ***320.*** A dashed line is provided illustrating a projected location for the original cartilage surface ***312.*** Similar to the measurements made above, ratios between the various measurements can be calculated.

[060] Turning now to **FIG. 3F,** an area of bone marrow edema is shown on the femur ***330*** and the tibia ***332.*** The shaded area of edema can be measured on a T2-weighted MRI scan. Alternatively, the area can be measured on one or more slices. These measurements can then be extended along the entire joint using multiple slices or a 3D acquisition. From these measurements volume can be determined or derived.

[061] **FIG. 3G** shows an area of subchondral sclerosis in the acetabulum ***340*** and the femur ***342***. The sclerosis can be measured on, for example, a T1 or T2-weighted MRI scan or on a CT scan. The area can be measured on one or more slices. Thereafter the measurement can be extended along the entire joint using multiple slices or a 3D acquisition. From these values a volume can be derived of the subchondral sclerosis. For purposes of illustration, a single sclerosis has been shown on each surface. However, a person of skill in the art will appreciate that more than one sclerosis can occur on a single joint surface.

[062] **FIG.3H** shows osteophytes on the femur ***350*** and the tibia ***352.*** The osteophytes are shown as cross-hatched areas. Similar to the sclerosis shown in **FIG. 3G,** the osteophytes can be measured on, for example, a T1 or T2-weighted MRI scan or on a CT scan. The area can be measured on one or more slices. Thereafter the measurement can be extended along the entire joint using multiple slices or a 3D acquisition. From these values a volume can be derived of the osteophytes. Additionally, a single osteophyte ***354*** or osteophyte groups ***356*** can be included in any measurement. Persons of skill in the art will appreciate that groups can be taken from a single joint surface or from opposing joint surfaces, as shown, without departing from the scope of the invention.

[063] Turning now to **FIG. 3I** an area of subchondral cysts ***360, 362, 364*** is shown. Similar to the sclerosis shown in **FIG. 3G**, the cysts can be measured on, for example, a T1 or T2-weighted MRI scan or on a CT scan. The area can be measured on one or more slices. Thereafter the measurement can be extended along the entire joint using multiple slices or a 3D acquisition. From these values a volume can be derived of the cysts. Additionally, single cysts ***366*** or groups of cysts ***366'*** can be included in any measurement. Persons of skill in the art will appreciate that groups can be taken from a single joint surface, as shown, or from opposing joint surfaces without departing from the scope of the invention.

[064] **FIG. 3J** illustrates an area of torn meniscal tissue (cross-hatched) ***372, 374*** as seen from the top ***370*** and in cross-section ***371.*** Again, similar to the sclerosis shown in **FIG. 3G**, the torn meniscal tissue can be measured on, for example, a T1 or T2-weighted MRI scan or on a CT scan. The area can be measured on one or more slices. Thereafter the measurement can be extended along the entire joint using multiple slices or a 3D acquisition. From these values a volume can be derived of the tear. Ratios such as surface or volume of torn to normal meniscal tissue can be derived as well as ratios of surface of torn meniscus to surface of opposing articulating surface.

[065] As shown in **FIG. 4A**, the process of optionally locating a ROI ***100***, extracting image data from the ROI ***102***, and deriving quantitative and/or qualitative image data from the extracted image data ***120***, can be repeated ***122***. Alternatively, or in addition, the process of locating a ROI ***100,*** can be repeated ***124.*** A person of skill in the art will appreciate that these steps can be repeated one or more times in any appropriate sequence, as desired, to obtain a sufficient amount of quantitative and/or qualitative data on the ROI or to separately extract or evaluate parameters. Further, the ROI used can be the same ROI as used in the first process or a newly identified ROI in the image. Additionally, as with **FIG. 1A** the steps of locating a region of interest ***100***, obtaining image data ***102,*** and deriving quantitative and/or qualitative image data can be repeated one or more times, as desired, ***101, 103, 121***, respectively. Although not depicted here, as discussed above with respect to **FIG. 1A**, the additional step of locating a part of the body for study ***98*** can be performed prior to locating a region of interest ***100*** without departing from the invention. Additionally that step can be repeated ***99.***

[066] **FIG. 4B** illustrates the process shown in **FIG. 4A** with the additional step enhancing image data ***104.*** Additionally, the step of enhancing image data ***104*** can be

repeated one or more times ***105***, as desired. The process of enhancing image data ***104*** can be repeated ***126*** one or more times as desired.

[067] Turning now to **FIG. 5A**, a process is shown whereby a region of interest is optionally located ***100***. Although not depicted here, as discussed above with respect to **FIG. 1A**, the step of locating a part of the body for study ***98*** can be performed prior to locating a region of interest ***100*** without departing from the invention. Additionally that step can be repeated ***99.*** Once the region of interest is located ***100***, and image data is extracted from the ROI ***102***, the extracted image data can then be converted to a 2D pattern ***130***, a 3D pattern ***132*** or a 4D pattern ***133***, for example including velocity or time, to facilitate data analyses. Following conversion to 2D ***130,*** 3D ***132*** or 4D pattern ***133*** the images are evaluated for patterns ***140***. Additionally images can be converted from 2D to 3D ***131,*** or from 3D to 4D ***131',*** if desired. Although not illustrated to avoid obscuring the figure, persons of skill in the art will appreciate that similar conversions can occur between 2D and 4D in this process or any process illustrated in this invention.

[068] As will be appreciated by those of skill in the art, the conversion step is optional and the process can proceed directly from extracting image data from the ROI ***102*** to evaluating the data pattern ***140*** directly ***134***. Evaluating the data for patterns, includes, for example, performing the measurements described in Table 1,Table 2 or Table 3, above.

[069] Additionally, the steps of locating the region of interest ***100,*** obtaining image data ***102,*** and evaluating patterns ***141*** can be performed once or a plurality of times, ***101, 103, 141,*** respectively at any stage of the process. As will be appreciated by those of skill in the art, the steps can be repeated. For example, following an evaluation of patterns ***140***, additional image data can be obtained ***135,*** or another region of interest can be located ***137***. These steps can be repeated as often as desired, in any combination desirable to achieve the data analysis desired.

[070] **FIG. 5B** illustrates an alternative process to that shown in **FIG. 5A** which includes the step of enhancing image data ***104*** prior to converting an image or image data to a 2D ***130,*** 3D ***132,*** or 4D ***133*** pattern. The process of enhancing image data ***104,*** can be repeated ***105*** if desired. **FIG. 5C** illustrates an alternative embodiment to the process shown in **FIG. 5B**. In this process, the step of enhancing image data ***104*** occurs after

converting an image or image data to a 2D ***130,*** 3D ***132,*** or 4D ***133*** pattern. Again, the process of enhancing image data ***104,*** can be repeated ***105*** if desired.

[071] **FIG. 5D** illustrates an alternative process to that shown in **FIG. 5A**. After locating a part of the body for study ***98*** and imaging, the image is then converted to a 2D pattern ***130,*** 3D pattern ***132*** or 4D pattern ***133.*** The region of interest ***100*** is optionally located within the image after conversion to a 2D, 3D or 4D image and data is then extracted ***102***. Patterns are then evaluated in the extracted image data ***140.*** As with the process of **FIG. 5A**, the conversion step is optional. Further, if desired, images can be converted between 2D, 3D ***131*** and 4D ***131'*** if desired.

[072] Similar to **FIG. 5A**, some or all the processes can be repeated one or more times as desired. For example, locating a part of the body for study ***98***, locating a region of interest ***100***, obtaining image data ***102***, and evaluating patterns ***140***, can be repeated one or more times if desired, ***99, 101, 103, 141,*** respectively. Again steps can be repeated. For example, following an evaluation of patterns ***140***, additional image data can be obtained ***135,*** or another region of interest can be located ***137*** and/or another portion of the body can be located for study ***139.*** These steps can be repeated as often as desired, in any combination desirable to achieve the data analysis desired.

[073] **FIG. 5E** illustrates an alternative process to that shown in **FIG. 5D**. In this process image data can be enhanced ***104.*** The step of enhancing image data can occur prior to conversion ***143***, prior to locating a region of interest ***145***, prior to obtaining image data ***102,*** or prior to evaluating patterns ***149***.

[074] Similar to **FIG. 5A**, some or all the processes can be repeated one or more times as desired, including the process of enhancing image data ***104***, which is shown as ***105.***

[075] The method also comprises obtaining an image of a bone or a joint, optionally converting the image to a two-dimensional or three-dimensional or four-dimensional pattern, and evaluating the amount or the degree of normal, diseased or abnormal tissue or the degree of degeneration in a region or a volume of interest using one or more of the parameters specified in Table 1, Table 2 and/or Table 3. By performing this method at an initial time T_1, information can be derived that is useful for diagnosing one or more conditions or for staging, or determining, the severity of a condition. This information can also be useful for determining the prognosis of a patient, for example with

osteoporosis or arthritis. By performing this method at an initial time T_1, and a later time T_2, the change, for example in a region or volume of interest, can be determined which then facilitates the evaluation of appropriate steps to take for treatment. Moreover, if the subject is already receiving therapy or if therapy is initiated after time T_1, it is possible to monitor the efficacy of treatment. By performing the method at subsequent times, T_2-T_n. additional data ca be acquired that facilitate predicting the progression of the disease as well as the efficacy of any interventional steps that have been taken. As will be appreciated by those of skill in the art, subsequent measurements can be taken at regular time intervals or irregular time intervals, or combinations thereof. For example, it can be desirable to perform the analysis at T_1 with an initial follow-up, T_2, measurement taken one month later. The pattern of one month follow-up measurements could be performed for a year (12 one-month intervals) with subsequent follow-ups performed at 6 month intervals and then 12 month intervals. Alternatively, as an example, three initial measurements could be at one month, followed by a single six month follow up which is then followed again by one or more one month follow-ups prior to commencing 12 month follow ups. The combinations of regular and irregular intervals are endless, and are not discussed further to avoid obscuring the invention.

[076] Moreover, one or more of the parameters listed in Tables 1, 2 and 3 can be measured. The measurements can be analyzed separately or the data can be combined, for example using statistical methods such as linear regression modeling or correlation. Actual and predicted measurements can be compared and correlated.

[077] The method for assessing the condition of a bone or joint in a subject can be fully automated such that the measurements of one or more of the parameters specified in Table 1, Table 2 or Table 3 are done automatically without intervention. The automatic assessment then can include the steps of diagnosis, staging, prognostication or monitoring the disease or diseases, or to monitor therapy. As will be appreciated by those of skill in the art, the fully automated measurement is, for example, possible with image processing techniques such as segmentation and registration. This process can include, for example, seed growing, thresholding, atlas and model based segmentation methods, live wire approaches, active and/or deformable contour approaches, contour tracking, texture based segmentation methods, rigid and non-rigid surface or volume registration, for example based on mutual information or other similarity measures. One skilled in the

art will readily recognize other techniques and methods for fully automated assessment of the parameters and measurements specified in Table 1, Table 2 and Table 3.

[078] Alternatively, the method of assessing the condition of a bone or joint in a subject can be semi-automated such that the measurements of one or more of the parameters, such as those specified in Table 1, are performed semi-automatically, i.e., with intervention. The semi-automatic assessment then allows for human interaction and, for example, quality control, and utilizing the measurement of said parameter(s) to diagnose, stage, prognosticate or monitor a disease or to monitor a therapy. The semi-automated measurement is, for example, possible with image processing techniques such as segmentation and registration. This can include seed growing, thresholding, atlas and model based segmentation methods, live wire approaches, active and/or deformable contour approaches, contour tracking, texture based segmentation methods, rigid and non-rigid surface or volume registration, for example base on mutual information or other similarity measures. One skilled in the art will readily recognize other techniques and methods for semi-automated assessment of the parameters specified in Table 1, Table 2 or Table 3.

[079] Turning now to **FIG. 6A**, a process is shown whereby the user locates a ROI ***100***, extracts image data from the ROI ***102***, and then derives quantitative and/or qualitative image data from the extracted image data ***120***, as shown above with respect to **FIG. 1**. Following the step of deriving quantitative and/or qualitative image data, a candidate agent is administered to the patient ***150.*** The candidate agent can be any agent the effects of which are to be studied. Agents can include any substance administered or ingested by a subject, for example, molecules, pharmaceuticals, biopharmaceuticals, agropharmaceuticals, or combinations thereof, including cocktails, that are thought to affect the quantitative and/or qualitative parameters that can be measured in a region of interest. These agents are not limited to those intended to treat disease that affects the musculoskeletal system but this invention is intended to embrace any and all agents regardless of the intended treatment site. Thus, appropriate agents are any agents whereby an effect can be detected via imaging. The steps of locating a region of interest ***100,*** obtaining image data ***102,*** obtaining quantitative and/or qualitative data from image data ***120***, and administering a candidate agent ***150***, can be repeated one or more times as desired, ***101, 103, 121, 151,*** respectively.

[080] **FIG. 6B** shows the additional step of enhancing image data ***104***, which can also be optionally repeated ***105*** as often as desired.

[081] As shown in **FIG. 6C** these steps can be repeated one or more times ***152*** to determine the effect of the candidate agent. As will be appreciated by those of skill in the art, the step of repeating can occur at the stage of locating a region of interest ***152*** as shown in **FIG. 6B** or it can occur at the stage obtaining image data ***153*** or obtaining quantitative and/or qualitative data from image data ***154*** as shown in **FIG. 6D**.

[082] **FIG. 6E** shows the additional step of enhancing image data ***104***, which can optionally be repeated ***105***, as desired.

[083] As previously described, some or all the processes shown in **FIGS. 6A-E** can be repeated one or more times as desired. For example, locating a region of interest ***100***, obtaining image data ***102***, enhancing image data ***104***, obtaining quantitative and/or qualitative data ***120***, evaluating patterns ***140***, and administering candidate agent ***150*** can be repeated one or more times if desired, ***101, 103, 105, 121, 141, 151*** respectively.

[084] In the scenario described in relation to **FIGS. 6,** an image is taken prior to administering the candidate agent. However, as will be appreciated by those of skill in the art, it is not always possible to have an image prior to administering the candidate agent. In those situations, progress is determined over time by evaluating the change in parameters from extracted image to extracted image.

[085] Turning now to **FIG. 7A,** the process is shown whereby the candidate agent is administered first ***150***. Thereafter a region of interest is located in an image taken ***100*** and image data is extracted ***102.*** Once the image data is extracted, quantitative and/or qualitative data is extracted from the image data ***120***. In this scenario, because the candidate agent is administered first, the derived quantitative and/or qualitative data derived is compared to a database ***160*** or a subset of the database which includes data for subjects having similar tracked parameters. As shown in **FIG. 7B** following the step of obtaining image data, the image data can be enhanced ***104***. This process can optionally be repeated ***105,*** as desired.

[086] Alternatively, as shown in **FIG. 7C** the derived quantitative and/or qualitative information can be compared to an image taken at T1 ***162,*** or any other time, if such

image is available. As shown in **FIG. 7D** the step of enhancing image data ***104*** can follow the step of obtaining image data ***102.*** Again, the process can be repeated ***105***, as desired.

[087] As previously described, some or all the processes illustrated in **FIGS. 7A-D** can be repeated one or more times as desired. For example, locating a region of interest ***100***, obtaining image data ***102***, enhancing image data ***104***, obtaining quantitative and/or qualitative data ***120***, administering candidate agent ***150,*** comparing quantitative and/or qualitative information to a database ***160,*** comparing quantitative and/or qualitative information to an image taken at a prior time, such as T_1, ***162,*** monitoring therapy ***170,*** monitoring disease progress ***172,*** predicting disease course ***174*** can be repeated one or more times if desired, ***101, 103, 105, 121, 151, 161, 163, 171, 173, 175*** respectively. Each of these steps can be repeated in one or more loops as shown in **FIG. 7B**, ***176, 177, 178, 179, 180***, as desired or appropriate to enhance data collection.

[088] Turning now to **FIG. 8A**, following the step of extracting image data from the ROI ***102,*** the image can be transmitted ***180.*** Transmission can be to another computer in the network or via the World Wide Web to another network. Following the step of transmitting the image ***180***, the image is converted to a pattern of normal and diseased tissue ***190*** Normal tissue includes the undamaged tissue located in the body part selected for study. Diseased tissue includes damaged tissue located in the body part selected for study. Diseased tissue can also include, or refer to, a lack of normal tissue in the body part selected for study. For example, damaged or missing cartilage would be considered diseased tissue. Once the image is converted, it is analyzed ***200***. **FIG. 8B** illustrates the process shown in **FIG. 8A** with the additional step of enhancing image data ***104***. As will be appreciated by those of skill in the art, this process can be repeated ***105*** as desired.

[089] As shown in **FIG. 8C**, the step of transmitting the image ***180*** illustrated in **FIG. 8A** is optional and need not be practiced under the invention. As will be appreciated by those of skill in the art, the image can also be analyzed prior to converting the image to a pattern of normal and diseased. **FIG. 8D** illustrates the process shown in **FIG. 8C** with the additional step of enhancing image data ***104*** which is optionally repeated ***105***, as desired.

[090] As previously described, some or all the processes in **FIGS. 8A-D** can be repeated one or more times as desired. For example, locating a region of interest ***100***, obtaining image data ***102***, enhancing image data ***104***,transmitting an image ***180,*** converting the image to a pattern of normal and diseased ***190,*** analyzing the converted

image ***200,*** can be repeated one or more times if desired, ***101, 103, 105, 181, 191, 201*** respectively.

[091] **FIG. 9** shows two devices ***900, 920*** that are connected. Either the first or second device can develop a degeneration pattern from an image of a region of interest ***905***. Similarly, either device can house a database for generating additional patterns or measurements ***915***. The first and second devices can communicate with each other in the process of analyzing an image, developing a degeneration pattern from a region of interest in the image, and creating a dataset of patterns or measurements or comparing the degeneration pattern to a database of patterns or measurements. However, all processes can be performed on one or more devices, as desired or necessary.

[092] In this method the electronically generated, or digitized image or portions of the image can be electronically transferred from a transferring device to a receiving device located distant from the transferring device; receiving the transferred image at the distant location; converting the transferred image to a pattern of normal or diseased or abnormal tissue using one or more of the parameters specified in Table 1, Table 2 or Table 3; and optionally transmitting the pattern to a site for analysis. As will be appreciated by those of skill in the art, the transferring device and receiving device can be located within the same room or the same building. The devices can be on a peer-to-peer network, or an intranet. Alternatively, the devices can be separated by large distances and the information can be transferred by any suitable means of data transfer, including the World Wide Web and ftp protocols.

[093] Alternatively, the method can comprise electronically transferring an electronically-generated image or portions of an image of a bone or a joint from a transferring device to a receiving device located distant from the transferring device; receiving the transferred image at the distant location; converting the transferred image to a degeneration pattern or a pattern of normal or diseased or abnormal tissue using one or more of the parameters specified in Table 1, Table 2 or Table 3; and optionally transmitting the degeneration pattern or the pattern of normal or diseased or abnormal tissue to a site for analysis.

[094] Another aspect of the invention is a kit for aiding in assessing the condition of a bone or a joint of a subject, which kit comprises a software program, which when installed and executed on a computer reads a degeneration pattern or a pattern of normal

or diseased or abnormal tissue derived using one or more of the parameters specified in Table 1, Table 2 or Table 3 presented in a standard graphics format and produces a computer readout. The kit can further include a database of measurements for use in calibrating or diagnosing the subject. One or more databases can be provided to enable the user to compare the results achieved for a specific subject against, for example, a wide variety of subjects, or a small subset of subjects having characteristics similar to the subject being studied.

[095] A system is provided that includes (a) a device for electronically transferring a degeneration pattern or a pattern of normal, diseased or abnormal tissue for the bone or the joint to a receiving device located distant from the transferring device; (b) a device for receiving said pattern at the remote location; (c) a database accessible at the remote location for generating additional patterns or measurements for the bone or the joint of the human wherein the database includes a collection of subject patterns or data, for example of human bones or joints, which patterns or data are organized and can be accessed by reference to characteristics such as type of joint, gender, age, height, weight, bone size, type of movement, and distance of movement; (d) optionally a device for transmitting the correlated pattern back to the source of the degeneration pattern or pattern of normal, diseased or abnormal tissue.

[096] Thus, the methods and systems described herein make use of collections of data sets of measurement values, for example measurements of bone structure and/or bone mineral density from x-ray images. Records can be formulated in spreadsheet-like format, for example including data attributes such as date of x-ray, patient age, sex, weight, current medications, geographic location, etc. The database formulations can further comprise the calculation of derived or calculated data points from one or more acquired data points, typically using the parameters listed in Tables 1, 2 and 3 or combinations thereof. A variety of derived data points can be useful in providing information about individuals or groups during subsequent database manipulation, and are therefore typically included during database formulation. Derived data points include, but are not limited to the following: (1) maximum value, e.g. bone mineral density, determined for a selected region of bone or joint or in multiple samples from the same or different subjects; (2) minimum value, e.g. bone mineral density, determined for a selected region of bone or joint or in multiple samples from the same or different subjects; (3) mean value, e.g. bone mineral density, determined for a selected region of bone or joint or in multiple

samples from the same or different subjects; (4) the number of measurements that are abnormally high or low, determined by comparing a given measurement data point with a selected value; and the like. Other derived data points include, but are not limited to the following: (1) maximum value of a selected bone structure parameter, determined for a selected region of bone or in multiple samples from the same or different subjects; (2) minimum value of a selected bone structure parameter, determined for a selected region of bone or in multiple samples from the same or different subjects; (3) mean value of a selected bone structure parameter, determined for a selected region of bone or in multiple samples from the same or different subjects; (4) the number of bone structure measurements that are abnormally high or low, determined by comparing a given measurement data point with a selected value; and the like. Other derived data points will be apparent to persons of ordinary skill in the art in light of the teachings of the present specification. The amount of available data and data derived from (or arrived at through analysis of) the original data provides an unprecedented amount of information that is very relevant to management of bone-related diseases such as osteoporosis. For example, by examining subjects over time, the efficacy of medications can be assessed.

[097] Measurements and derived data points are collected and calculated, respectively, and can be associated with one or more data attributes to form a database. The amount of available data and data derived from (or arrived at through analysis of) the original data provide provides an unprecedented amount of information that is very relevant to management of musculoskeletal-related diseases such as osteoporosis or arthritis. For example, by examining subjects over time, the efficacy of medications can be assessed.

[098] Data attributes can be automatically input with the electronic image and can include, for example, chronological information (e.g., DATE and TIME). Other such attributes can include, but are not limited to, the type of imager used, scanning information, digitizing information and the like. Alternatively, data attributes can be input by the subject and/or operator, for example subject identifiers, i.e. characteristics associated with a particular subject. These identifiers include but are not limited to the following: (1) a subject code (e.g., a numeric or alpha-numeric sequence); (2) demographic information such as race, gender and age; (3) physical characteristics such as weight, height and body mass index (BMI); (4) selected aspects of the subject's medical history (e.g., disease states or conditions, etc.); and (5) disease-associated

characteristics such as the type of bone disorder, if any; the type of medication used by the subject. In the practice of the present invention, each data point would typically be identified with the particular subject, as well as the demographic, etc. characteristic of that subject.

[099] Other data attributes will be apparent to persons of ordinary skill in the art in light of the teachings of the present specification. (See, also, WO 02/30283, incorporated by reference in its entirety herein).

[0100] Thus, data (*e.g.,* bone structural information or bone mineral density information or articular information) is obtained from normal control subjects using the methods described herein. These databases are typically referred to as "reference databases" and can be used to aid analysis of any given subject's x-ray image, for example, by comparing the information obtained from the subject to the reference database. Generally, the information obtained from the normal control subjects will be averaged or otherwise statistically manipulated to provide a range of "normal" measurements. Suitable statistical manipulations and/or evaluations will be apparent to those of skill in the art in view of the teachings herein. The comparison of the subject's x-ray information to the reference database can be used to determine if the subject's bone information falls outside the normal range found in the reference database or is statistically significantly different from a normal control.

[0101] Data obtained from images, as described above, can be manipulated, for example, using a variety of statistical analyses to produce useful information. Databases can be created or generated from the data collected for an individual, or for a group of individuals, over a defined period of time (e.g., days, months or years), from derived data, and from data attributes.

[0102] For example, data can be aggregated, sorted, selected, sifted, clustered and segregated by means of the attributes associated with the data points. A number of data mining software exist which can be used to perform the desired manipulations.

[0103] Relationships in various data can be directly queried and/or the data analyzed by statistical methods to evaluate the information obtained from manipulating the database.

[0104] For example, a distribution curve can be established for a selected data set, and the mean, median and mode calculated therefor. Further, data spread characteristics, e.g., variability, quartiles, and standard deviations can be calculated.

[0105] The nature of the relationship between any variables of interest can be examined by calculating correlation coefficients. Useful methods for doing so include, but are not limited to: Pearson Product Moment Correlation and Spearman Rank Correlation. Analysis of variance permits testing of differences among sample groups to determine whether a selected variable has a discernible effect on the parameter being measured.

[0106] Non-parametric tests can be used as a means of testing whether variations between empirical data and experimental expectancies are attributable to chance or to the variable or variables being examined. These include the Chi Square test, the Chi Square Goodness of Fit, the 2x2 Contingency Table, the Sign Test and the Phi Correlation Coefficient. Other tests include z-scores, T-scores or lifetime risk for arthritis, cartilage loss or osteoporotic fracture.

[0107] There are numerous tools and analyses available in standard data mining software that can be applied to the analyses of the databases that can be created according to this invention. Such tools and analysis include, but are not limited to, cluster analysis, factor analysis, decision trees, neural networks, rule induction, data driven modeling, and data visualization. Some of the more complex methods of data mining techniques are used to discover relationships that are more empirical and data-driven, as opposed to theory driven, relationships.

[0108] Statistical significance can be readily determined by those of skill in the art. The use of reference databases in the analysis of x-ray images facilitates that diagnosis, treatment and monitoring of bone conditions such as osteoporosis.

[0109] For a general discussion of statistical methods applied to data analysis, see Applied Statistics for Science and Industry, by A. Romano, 1977, Allyn and Bacon, publisher.

[0110] The data is preferably stored and manipulated using one or more computer programs or computer systems. These systems will typically have data storage capability (*e.g.,* disk drives, tape storage, optical disks, etc.). Further, the computer systems can be networked or can be stand-alone systems. If networked, the computer system would be

able to transfer data to any device connected to the networked computer system for example a medical doctor or medical care facility using standard e-mail software, a central database using database query and update software (e.g., a data warehouse of data points, derived data, and data attributes obtained from a large number of subjects). Alternatively, a user could access from a doctor's office or medical facility, using any computer system with Internet access, to review historical data that can be useful for determining treatment.

[0111] If the networked computer system includes a World Wide Web application, the application includes the executable code required to generate database language statements, for example, SQL statements. Such executables typically include embedded SQL statements. The application further includes a configuration file that contains pointers and addresses to the various software entities that are located on the database server in addition to the different external and internal databases that are accessed in response to a user request. The configuration file also directs requests for database server resources to the appropriate hardware, as can be necessary if the database server is distributed over two or more different computers.

[0112] As a person of skill in the art will appreciate, one or more of the parameters specified in Table 1, Table 2 and Table 3 can be used at an initial time point T_1 to assess the severity of a bone disease such as osteoporosis or arthritis. The patient can then serve as their own control at a later time point T_2, when a subsequent measurement using one or more of the same parameters used at T_1 is repeated.

[0113] A variety of data comparisons can be made that will facilitate drug discovery, efficacy, dosing, and comparisons. For example, one or more of the parameters specified in Table 1, Table 2 and Table 3 can be used to identify lead compounds during drug discovery. For example, different compounds can be tested in animal studies and the lead compounds with regard to highest therapeutic efficacy and lowest toxicity, e.g. to the bone or the cartilage, can be identified. Similar studies can be performed in human subjects, e.g. FDA phase I, II or III trials. ,Alternatively, or in addition, one or more of the parameters specified in Table 1,Table 2 and Table 3 can be used to establish optimal dosing of a new compound. It will be appreciated also that one or more of the parameters specified in Table 1,Table 2 and Table 3 can be used to compare a new drug against one or more established drugs or a placebo.

[0114] The foregoing description of embodiments of the present invention has been provided for the purposes of illustration and description. It is not intended to be exhaustive or to limit the invention to the precise forms disclosed. Many modifications and variations will be apparent to the practitioner skilled in the art. The embodiments were chosen and described in order to best explain the principles of the invention and its practical application, thereby enabling others skilled in the art to understand the invention and the various embodiments and with various modifications that are suited to the particular use contemplated. It is intended that the scope of the invention be defined by the following claims and its equivalence.

WHAT IS CLAIMED IS:

1. A method for analyzing at least one of bone mineral density, bone structure and surrounding tissue comprising:

a. obtaining an image of a subject;

b. locating a region of interest on the image;

c. obtaining data from the region of interest; and

d. deriving data selected from the group of qualitative and quantitative from the image data obtained at step c.

2. A kit for aiding in the assessment of the condition of at least one of a bone and joint comprising:

a software program which reads at least one of a degeneration pattern, a pattern of normal tissue, a pattern of abnormal tissue, and a pattern of diseased tissue.

3. The kit of claim 2 further comprising a database of measurements for comparison to the at least one of degeneration pattern, pattern of normal tissue, pattern of abnormal tissue, and pattern of diseased tissue.

4. The kit of claim 2 further comprising a subset of a database of measurements for comparison to the at least one of degeneration pattern, pattern of normal tissue, pattern of abnormal tissue, and pattern of diseased tissue.

5. At least one of an automated and semi-automated method of using an imaging marker comprising:

obtaining image data from a subject;

obtaining data from the image data wherein the data obtained is at least one of quantitative and qualitative data; and

administering an agent.

6. The method of claim 5 wherein the one of the automated and semi-automated method is used for at least one of drug discovery, diagnosis, disease staging, disease monitoring, disease management, prognostication, therapy monitoring, drug efficacy monitoring, and disease prediction.

7. At least one of a system for monitoring the efficacy of an agent and a system for drug discovery comprising:

administering an agent to a subject;

obtaining image data; and

obtaining data from the image data wherein the data obtained is at least one

of quantitative and qualitative data.

8. At least one of a system for diagnosing a disease, determining disease staging, monitoring disease progression, managing a disease, disease prognostication, predicting a disease, monitoring therapy and randomizing a subject within a group of patients comprising:

a. obtaining image data of a subject;

b. obtaining data from the image data wherein the data obtained is at least one of quantitative and qualitative data; and

c. comparing the at least one of quantitative and qualitative data in step b to at least one of: a database of at least one of quantitative and qualitative data obtained from a group of subjects; at least one of quantitative and qualitative data obtained from the subject; and at least one of a quantitative and qualitative data obtained from the subject at time Tn.

9. The method of claims 1, 5, 7 and 8 further including the step of enhancing image data.

10. The method of claims 1, 5, 7 and 8 wherein the subject is a mammal.

11. The method of claims 1, 5, 7 and 8 wherein the subject is a human.

12. The method of claims 1, 5, 7 and 8 wherein the subject is a horse.

13. The method of claims 1, 5, 7 and 8 wherein the step of obtaining image data includes obtaining data from a measured parameter selected from the group consisting of: bone parameters, cartilage parameters, cartilage defect parameters, cartilage disease parameters, area parameters, and volume parameters.

14. The method of claims 1, 5, 7 and 8 wherein the step of obtaining image data includes extracting data from a measured parameter selected from the group consisting of:

a presence or absence of bone marrow edema;

a volume of bone marrow edema;

a volume of bone marrow edema normalized by at least one of width, area, size, and volume;

a presence or absence of osteophytes;

a presence or absence of subchondral cysts;

a presence or absence of subchondral sclerosis;

a volume of osteophytes; a volume of subchondral cysts;

a volume of subchondral sclerosis;

an area of bone marrow edema; an area of osteophytes;

an area of subchondral cysts;

an area of subchondral sclerosis;

a depth of bone marrow edema;

a depth of osteophytes;

a depth of subchondral cysts;

a depth of subchondral sclerosis;

at least one of a volume, area, and depth of at least one of an osteophytes, subchondral cysts, subchondral sclerosis wherein the at least one of volume, area, and depth is normalized by at least one of width, area, size, volume a bone proximal to at least one of the osteophyte, subchondral cyst, or subchondral sclerosis;

a presence or absence of meniscal tear;

a presence or absence of cruciate ligament tear;

a presence or absence of collateral ligament tear;

a volume of menisci;

a ratio of volume of normal to at least one of torn, damaged and degenerated meniscal tissue;

a ratio of surface area of normal to at least one of torn, damaged and degenerated meniscal tissue;

a ratio of surface area of normal to at least one of torn, damaged and degenerated meniscal tissue to total joint or cartilage surface area;

a ratio of surface area of at least one of torn, damaged and degenerated meniscal tissue to a total surface area of at least one of joint and cartilage;

a size ratio of opposing articular surfaces;

a meniscal subluxation/dislocation in millimeters;

an index combining different articular parameters ;

a 3D surface contour information of subchondral bone;

an actual or predicted knee flexion angle during gait cycle;

a predicted knee rotation during gait cycle;

a predicted knee displacement during gait cycle;

a predicted load bearing line on cartilage surface during gait cycle and measurement of distance between load bearing line and at least one of cartilage defect and diseased cartilage;

a predicted load bearing area on cartilage surface during gait cycle and measurement of distance between load bearing area and at least one of cartilage defect and diseased cartilage;

a predicted load bearing line on cartilage surface during standing or different degrees of knee flexion and extension and measurement of distance between load bearing line and at least one of cartilage defect and diseased cartilage;

a predicted load bearing area on cartilage surface during standing or different degrees of knee flexion and extension and measurement of distance between load bearing area and at least one of cartilage defect and diseased cartilage;

a ratio of load bearing area to area of at least one of cartilage defect and diseased cartilage;

a percentage of load bearing area affected by cartilage disease;

a location of cartilage defect within load bearing area;

a load applied to cartilage defect, area of diseased cartilage; and

a load applied to cartilage adjacent to at least one of cartilage defect and area of diseased cartilage.

15. The method of claim 14 wherein the index combining different articular parameters includes:

a presence or absence of cruciate or collateral ligament tear in the subject,

a body mass index for the subject,

a weight for the subject, or

a height for the subject.

16. The method of claims 1, 5, 7 and 8 wherein the image data is obtained from a hip and the step of obtaining image data includes extracting data from a measured parameter selected from the group consisting of:

microarchitecture parameters on structures parallel to stress lines;

microarchitecture parameters on structures perpendicular to stress lines;

geometry;

shaft angle ;

neck angle;

diameter of femur neck;

hip axis length;

largest cross-section of femur head;

average thickness of cortical within at least one ROI;

standard deviation of cortical thickness within at least one ROI;

maximum thickness of cortical within at least one ROI;

minimum thickness of cortical within at least one ROI; and

hip joint space width.

17. The method of claims 1, 5, 7 and 8 wherein the image data is obtained from a region of a spine and the step of obtaining image data includes extracting data from a measured parameter selected from the group consisting of:

microarchitecture parameters on vertical structures;

microarchitecture parameters on horizontal structures;

geometry;

superior endplate cortical thickness;

inferior endplate cortical thickness;

anterior vertebral wall cortical thickness;

posterior vertebral wall cortical thickness;

superior aspect of pedicle cortical thickness;

inferior aspect of pedicle cortical thickness;

vertebral height;

vertebral diameter;

pedicle thickness;

maximum vertebral height;

minimum vertebral height;

average vertebral height;

anterior vertebral height;

medial vertebral height;

posterior vertebral height;

maximum inter-vertebral height;

minimum inter-vertebral height; and

average inter-vertebral height.

18. The method of claims 1, 5, 7 and 8 wherein the image data is obtained from a region of a knee and the step of obtaining image data includes extracting data from a measured parameter selected from the group consisting of:

average medial joint space width;

minimum medial joint space width;

maximum medial joint space width;

average lateral joint space width;

minimum lateral joint space width; and

maximum lateral joint space width.

19. The method of claims 1, 5, 7 and 8 wherein the step of obtaining image data includes extracting bone parameters selected from the group consisting of:

stainless steel equivalent thickness wherein the stainless steel equivalent thickness is determined as the average gray value of the region of interest expressed as thickness of stainless steel with equivalent intensity;

trabecular contrast wherein the trabecular contrast is determined as one of the trabecular equivalent thickness and marrow equivalent thickness;

fractal dimension;

Fourier spectral analysis wherein the Fourier spectral analysis is determined as one of a mean transform coefficient absolute value and a mean spatial first moment;

predominant orientation of spatial energy spectrum;

at least one of trabecular area and total area;

trabecular perimeter;

trabecular distance transform;

marrow distance transform;

trabecular distance transform regional maxima values;

marrow distance transform regional maxima values;

star volume;

trabecular bone pattern factor ;

connected skeleton count or trees (T);

node count (N);

segment count (S);

node-to-node segment count (NN);

node-to-free-end segment count (NF);

node-to-node segment length (NNL)

node-to-free-end segment length (NFL);

free-end-to-free-end segment length (FFL);

node-to-node total struts length (NN.TSL);

free-end-to-free-ends total struts length(FF.TSL);

total struts length (TSL);

FF.TSL/ TSL;

NN.TSL/ TSL;

loop count (Lo);

loop area;

mean distance transform values for each connected skeleton;

mean distance transform values for each segment (Tb.Th);

mean distance transform values for each node-to-node segment (Tb.Th.NN);

mean distance transform values for each node-to-free-end segment (Tb.Th.NF);

orientation of each segment;

angle of each segment;

angle between segments;

length-thickness ratios (NNL/Tb.Th.NN) and (NFL/ Tb.Th.NF); and

interconnectivity index (ICI) ICI = (N * NN)/ (T * (NF + 1));

20. The method of claim 12 wherein total bone parameter factor is (P1 - P2) / (A1 - A2)

further wherein P1 and A1 are the perimeter length and trabecular bone area before dilation and P2 and A2 corresponding values after a single pixel dilation, measure of connectivity

21. The method of claims 1, 5, 7 and 8 wherein the step of obtaining image data includes extracting at least one of cartilage parameters, cartilage defect parameters, and diseased cartilage parameters, wherein the data extracted is selected from the group consisting of:

total cartilage volume;

focal cartilage volume;

a cartilage thickness distribution or thickness map;

mean cartilage thickness over substantially total surface;

mean cartilage thickness in focal area;

median cartilage thickness;

maximum cartilage thickness;

minimum cartilage thickness;

3D cartilage surface information;

cartilage curvature analysis;

volume of cartilage defect/diseased cartilage;

depth of cartilage defect/diseased cartilage;

area of cartilage defect/diseased cartilage;

at least one of 2D and 3D location of cartilage defect/diseased cartilage in the articular surface;

at least one of 2D and 3D location of cartilage defect/diseased cartilage in relationship to weight-bearing area;

a ratio of at least two of diameter of cartilage defect, diameter of diseased cartilage, and thickness of surrounding normal cartilage;

a ratio of at least two of depth of cartilage defect, depth of diseased cartilage and thickness of surrounding normal cartilage;

a ratio of at least two of volume of cartilage defect, volume of diseased cartilage and thickness of surrounding normal cartilage;

a ratio of at least two of surface area of cartilage defect, surface area of diseased cartilage and total joint surface area; and

a ratio of at least two of volume of cartilage defect, volume of diseased cartilage and total cartilage volume.

22. The method of claims 1, 5, 7 and 8 wherein the steps are performed automatically.

23. The method of claims 1, 5, 7 and 8 wherein the steps are performed semi-automatically.

24. The method of claims 1, 5, 7 and 8 wherein at least one of the steps of the method is performed on a first computer.

25. The method of claims 1, 5, 7 and 8 wherein at least one of the steps of the method is performed on a first computer and at least one of the steps of the method is performed on a second computer.

26. The method of claim 25 wherein the first computer and the second computer are connected.

27. The method of claim 26 wherein the first computer and the second computer are connected by one of a peer to peer network, direct link, intranet, and internet.

28. The method of claim 1 wherein the step of locating a region of interest is repeated.

29. The method of claims 1, 5, 7 and 8 wherein the step of obtaining image data from a region of interest is repeated.

30. The method of claims 1, 5, 7 and 8 wherein at least one of the image and image data is converted to a 2D pattern.

31. The method of claim 30 wherein the 2D pattern is evaluated.

32. The method of claim 30 wherein the 2D pattern is converted to a 3D pattern.

33. The method of claim 31 wherein the 2D pattern is converted to a 3D pattern.

34. The method of claim 30 wherein the 2D pattern is converted to a 4D pattern.

35. The method of claim 31 wherein the 2D pattern is converted to a 4D pattern.

36. The method of claim 33 wherein the 3D pattern is converted to a 4D pattern.

37. The method of claims 1, 5, 7 and 8 wherein at least one of the image and image data is converted to a 3D pattern.

38. The method of claim 37 wherein the 3D pattern is evaluated.

39. The method of claim 37 wherein the 3D pattern is converted to a 2D pattern.

40. The method of claim 39 wherein the 3D pattern is converted to a 2D pattern.

41. The method of claim 37 wherein the 3D pattern is converted to a 4D pattern.

42. The method of claim 38 wherein the 3D pattern is converted to a 4D pattern.

43. The method of claim 39 wherein the 2D pattern is converted to a 4D pattern.

44. The method of claims 1, 5, 7 and 8 wherein at least one of the image and image data is converted to a 4D pattern.

45. The method of claim 44 wherein the 4D pattern is evaluated.

46. The method of claim 1 further comprising the step of administering a candidate agent.

47. The method of claim 46 wherein the candidate agent is at least one agent selected from the group consisting of: substance administered to a subject, substance ingested by a subject, molecules, pharmaceuticals, biopharmaceuticals, agropharmaceuticals.

48. The method of claims 1, 5, 7 and 8 further comprising the step of comparing at least one of the image and image data to a database.

49. The method of claims 1, 5, 7 and 8 further comprising the step of comparing the at least one of the image and image data to a subset of a database.

50. The method of claims 1, 5, 7 and 8 further comprising the step of comparing at least one of quantitative data and qualitative data to an image taken at T1.

51. The method of claims 1, 5, 7 and 8 further comprising the step of comparing at least one of quantitative data and qualitative data to an image taken prior to the image under analysis.

52. The method of claims 1, 5, 7 and 8 further comprising the step of comparing at least one of quantitative data and qualitative data to an image taken at Tn.

53. The method of claim 1 further comprising the step of transmitting at least one of the image, data extracted from the region of interest.

54. The method of claims 1, 5, 7 and 8 wherein at least one of the image and image data is converted to at least one of a pattern of normal, a pattern of diseased, and a pattern of normal and diseased.

55. The method of claims 1, 5, 7 and 8 wherein at least one of obtaining image and image data includes measuring at least one of microarchitecture and macroanatomical structures.

56. The method of claim 55 further comprising measuring the average density.

57. The method of claim 56 wherein the average density measurement includes a calibrated density of the region of interest.

58. The method of claim 55 further comprising measuring microanatomical structures on at least one of dental, spine, hip, knee and bone core x-rays.

59. The method of claim 58 further comprising measuring at least one of:

calibrated density of extracted structures;

calibrated density of background;

average intensity of extracted structures;

average intensity of background area wherein the background area includes non-extracted structures;

structural contract wherein structural contrast is an average intensity of extracted structures divided by an average intensity of a background;

calibrated structural contrast wherein calibrated structural contrast is a calibrated density of extracted structures divided by a calibrated density of a background;

total area of extracted structures;

total area of a region of interest;

an area of extracted structures normalized by a total area of a region of interest;

a boundary length of an extracted area normalized by a total are of a region of interest;

a number of structures normalized by an area of a region of interest;

a trabecular bone pattern factor;

a measurement of concavity and convexity of structures;

a star volume of extracted structures;

a star volume of background; and

a number of loops normalized by an area of a region of interest.

60. The method of claim 55 further comprising measuring a distance transform of extracted structures.

61. The method of claim 60 wherein the measurement on the distance transform of extracted structures further comprises one or more of:

an average regional maximum thickness;

a standard deviation of regional maximum thickness;

a largest value of regional maximum thickness; and

a median regional maximum thickness.

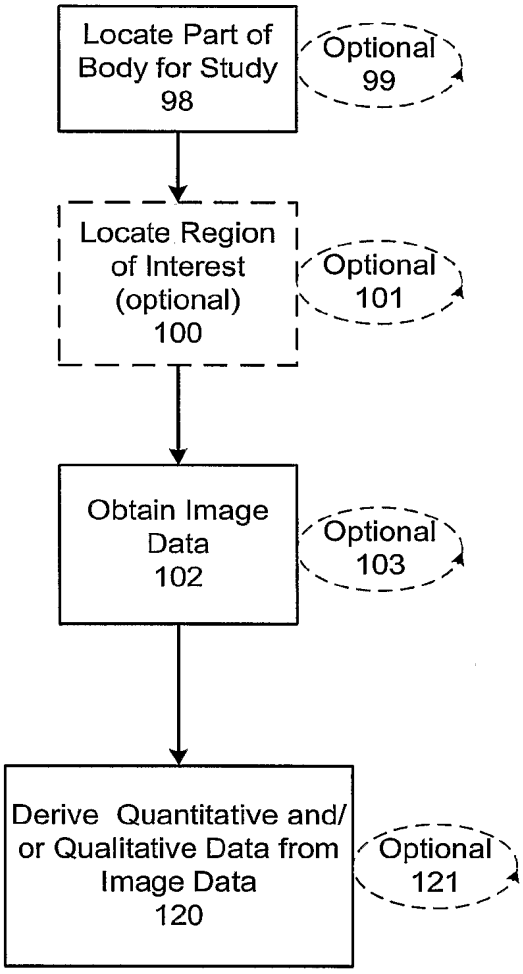
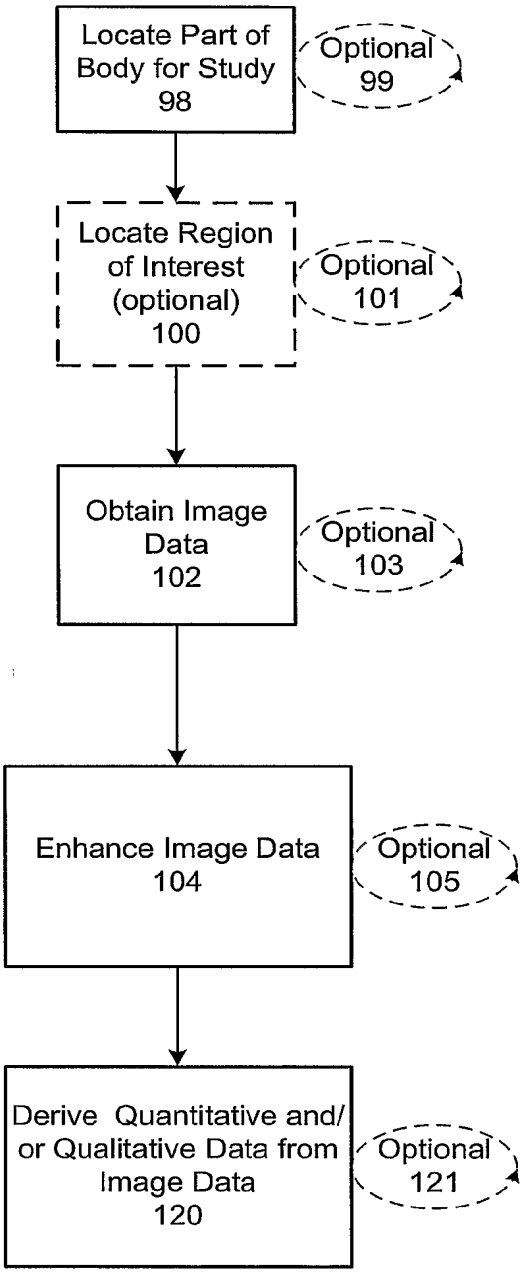

Locate Part of Body for Study 98
Optional 99
Locate Region of Interest (optional) 100
Optional 101
Obtain Image Data 102
Optional 103
Derive Quantitative and/or Qualitative Data from Image Data 120
Optional 121

FIG. 1A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Optional 99
Locate Region of Interest (optional) 100
Optional 101
Obtain Image Data 102
Optional 103
Enhance Image Data 104
Optional 105
Derive Quantitative and/or Qualitative Data from Image Data 120
Optional 121

FIG. 1B

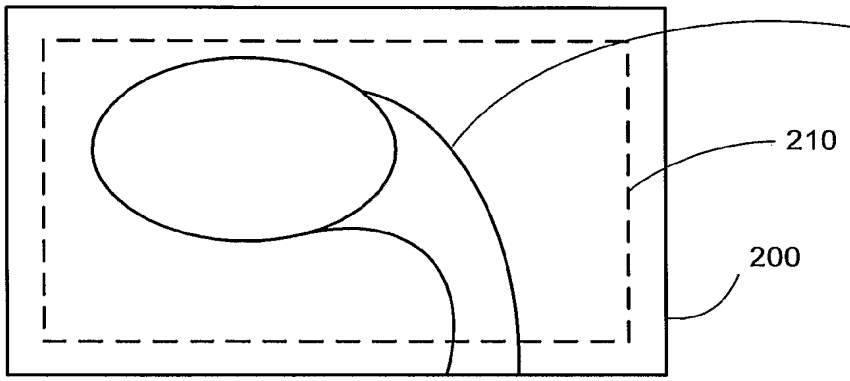


FIG. 2A

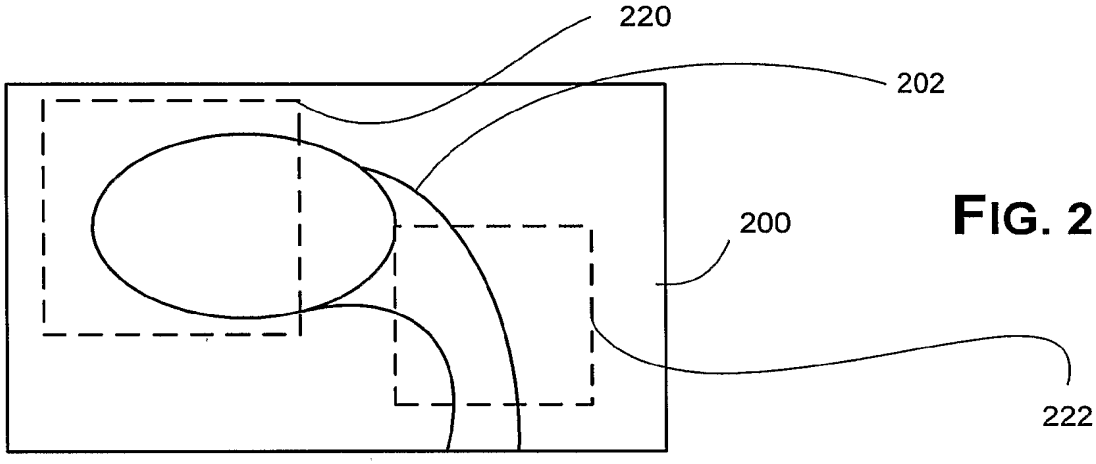


FIG. 2B

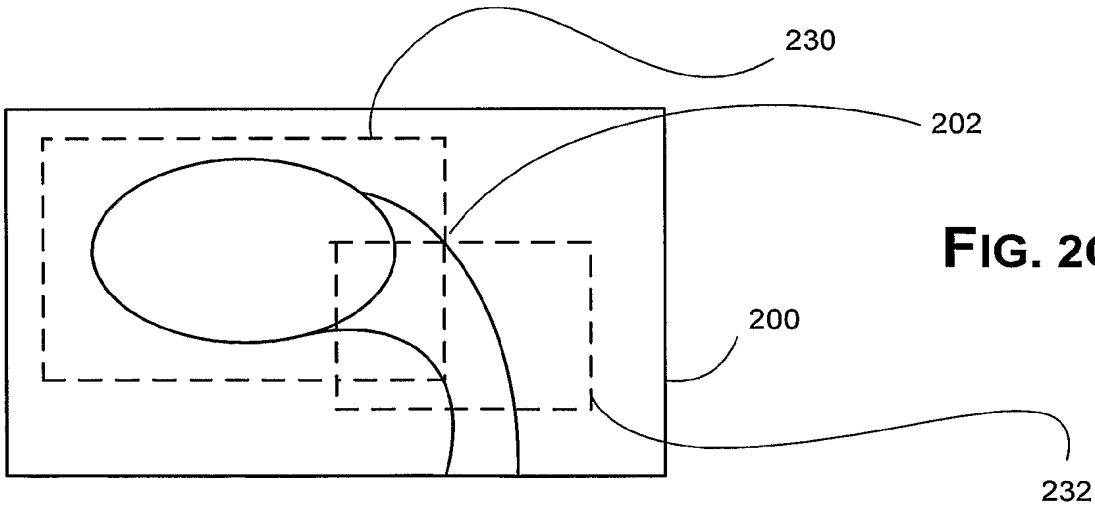


FIG. 2C

FIG. 3A

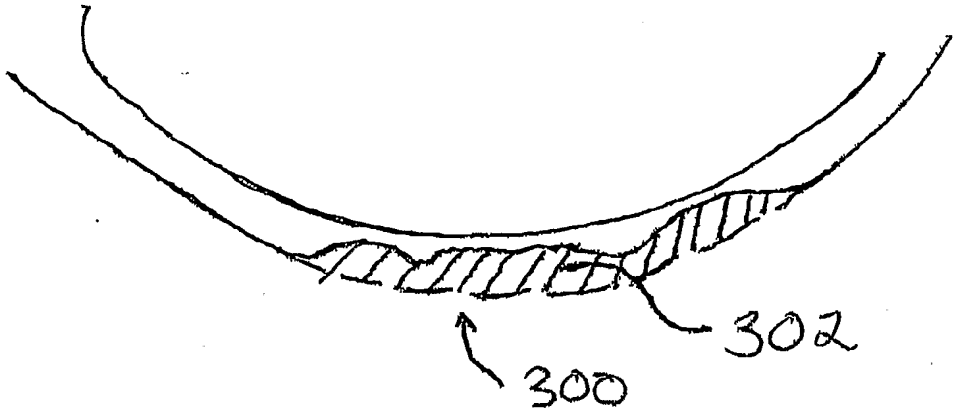
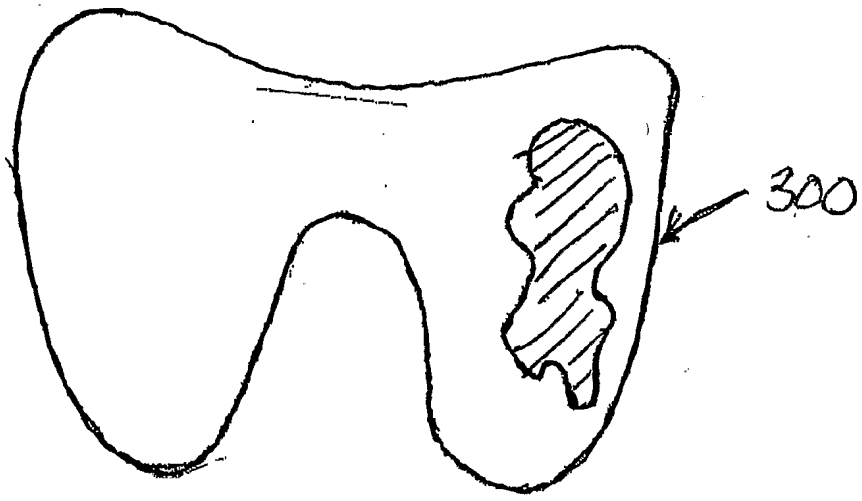


FIG. 3B



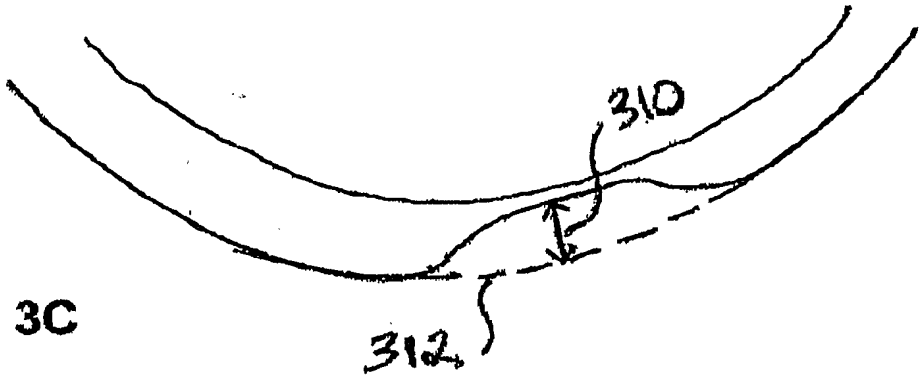


FIG. 3C

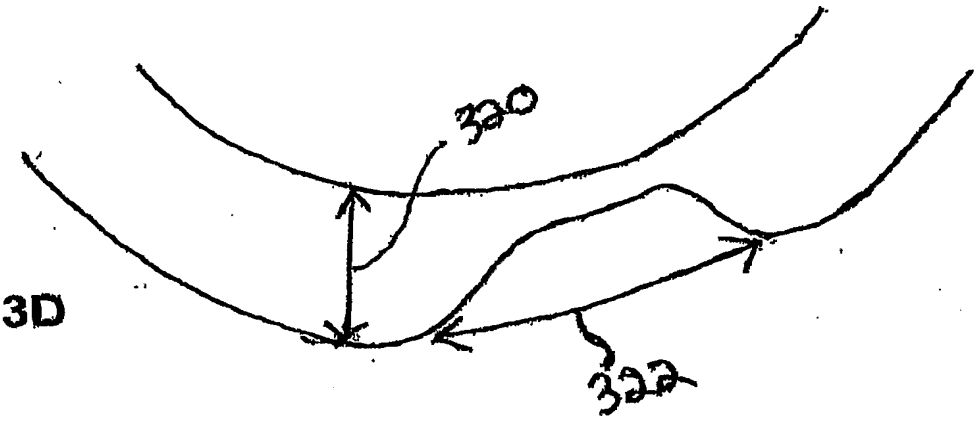


FIG. 3D

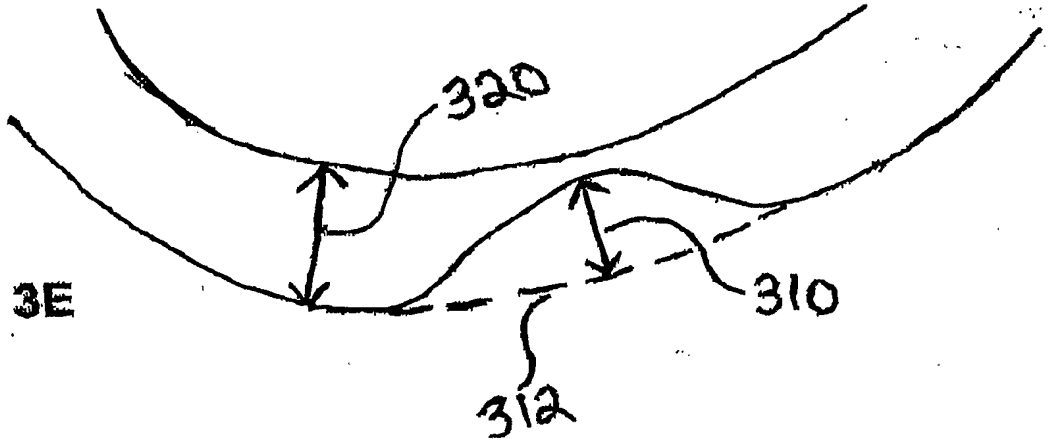


FIG. 3E

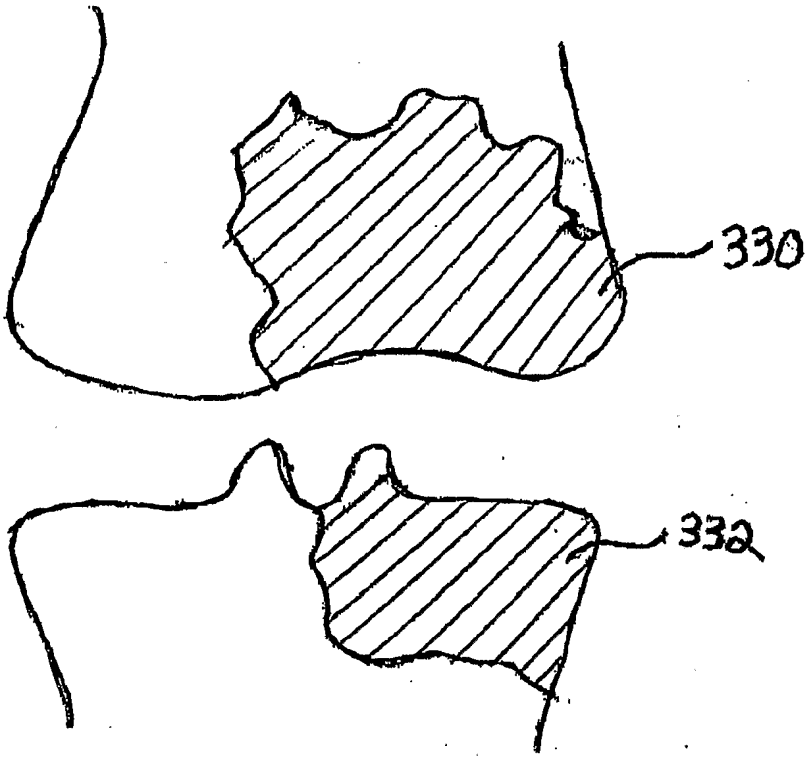


FIG. 3F

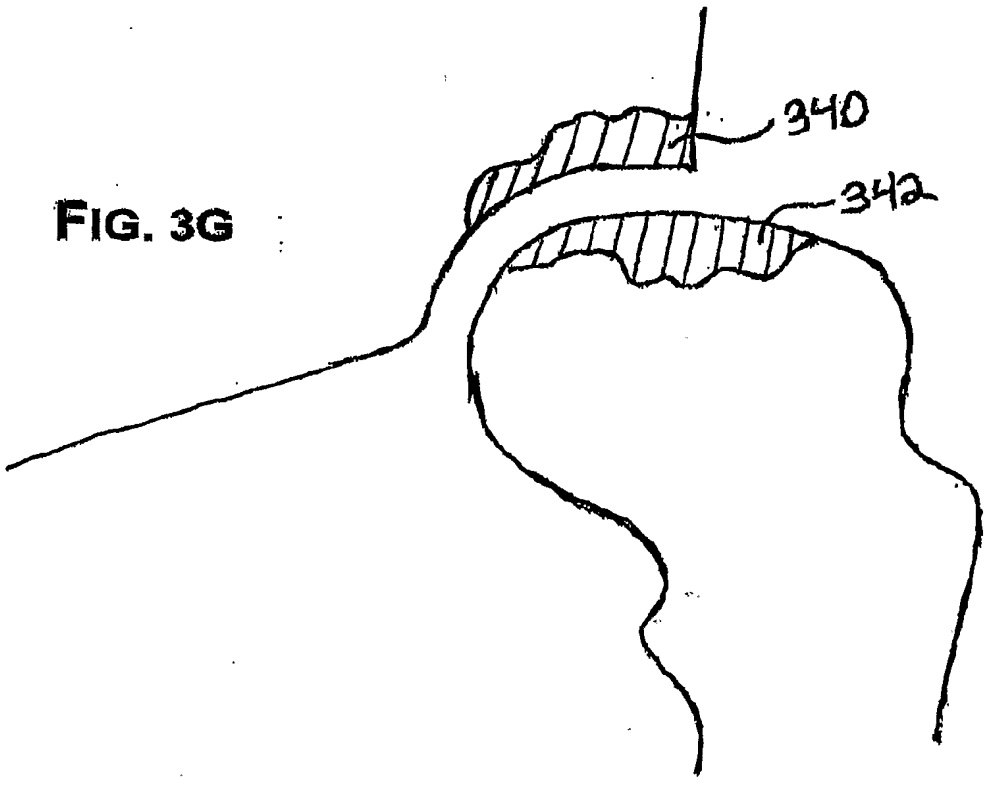
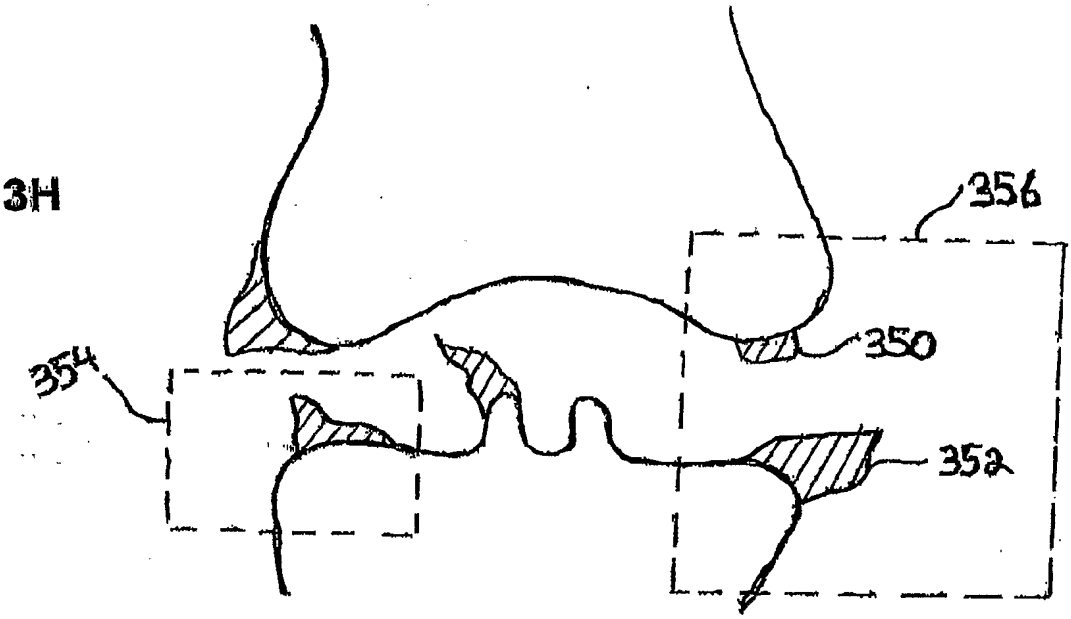


FIG. 3G

FIG. 3H



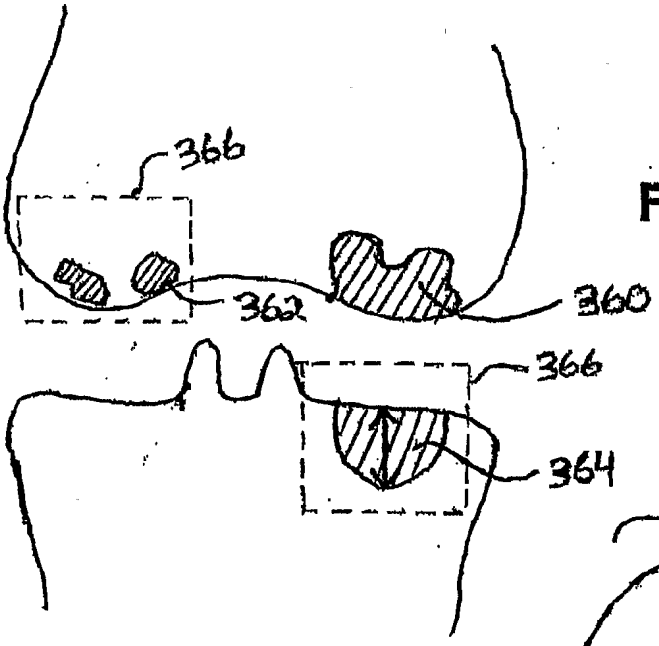


FIG. 3I

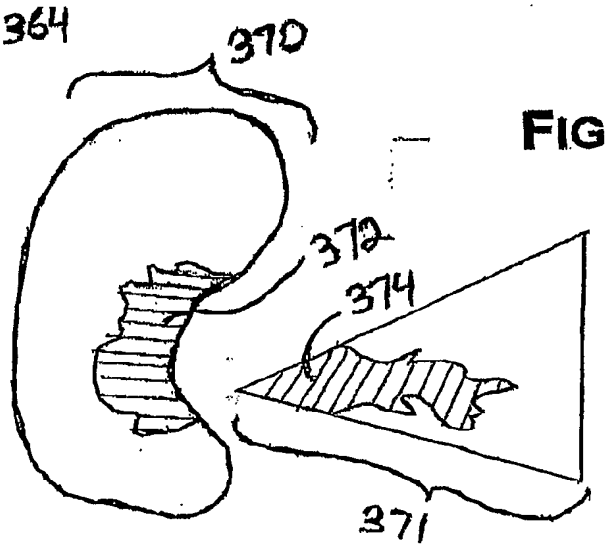


FIG. 3J

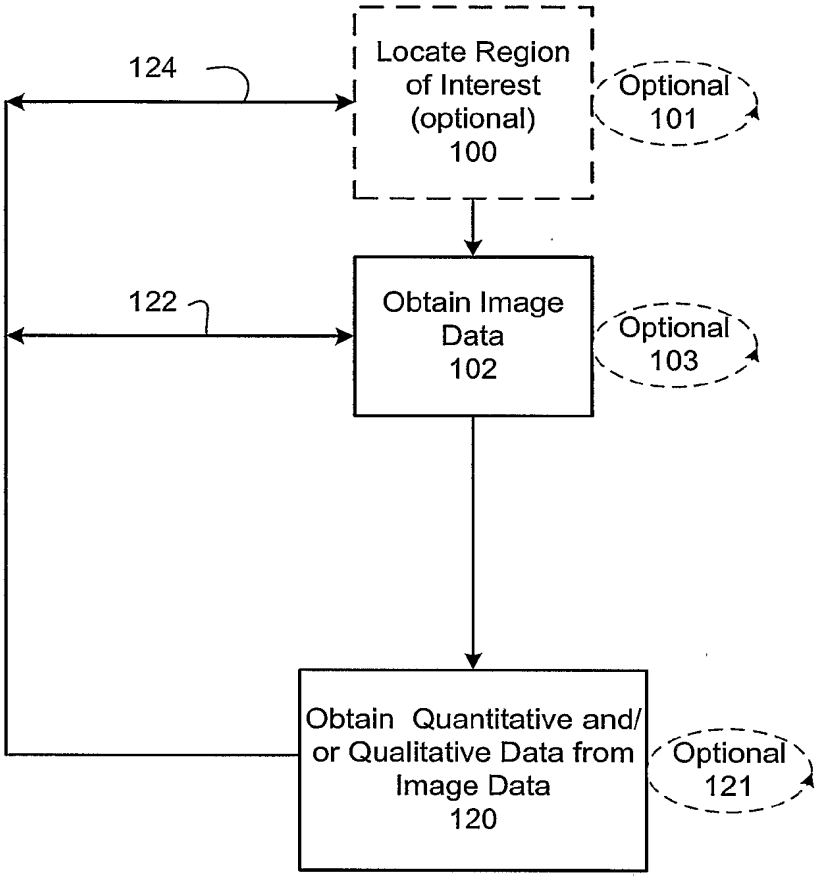

124
Locate Region of Interest (optional) 100
Optional 101
122
Obtain Image Data 102
Optional 103
Obtain Quantitative and/or Qualitative Data from Image Data 120
Optional 121

FIG. 4A

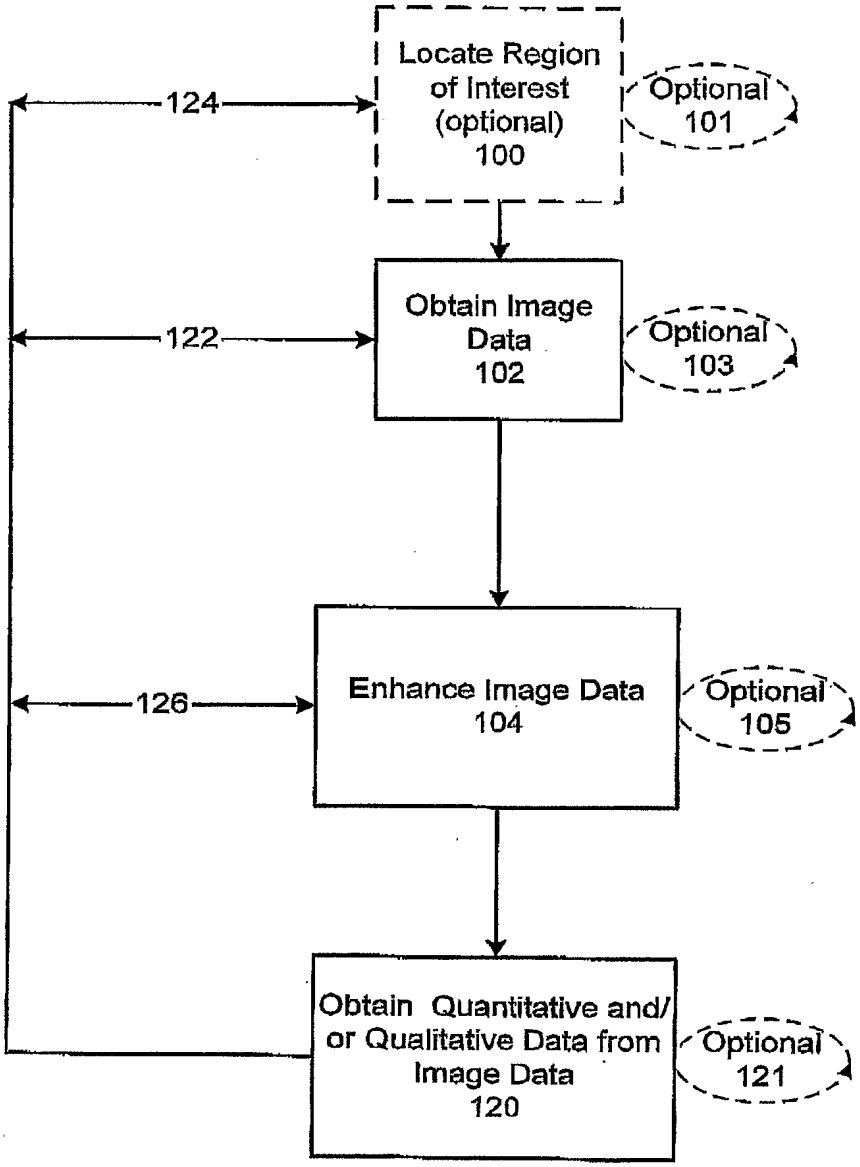

Locate Region of Interest (optional) 100
Optional 101
124
Obtain Image Data 102
Optional 103
122
Enhance Image Data 104
Optional 105
126
Obtain Quantitative and/or Qualitative Data from Image Data 120
Optional 121

FIG. 4B

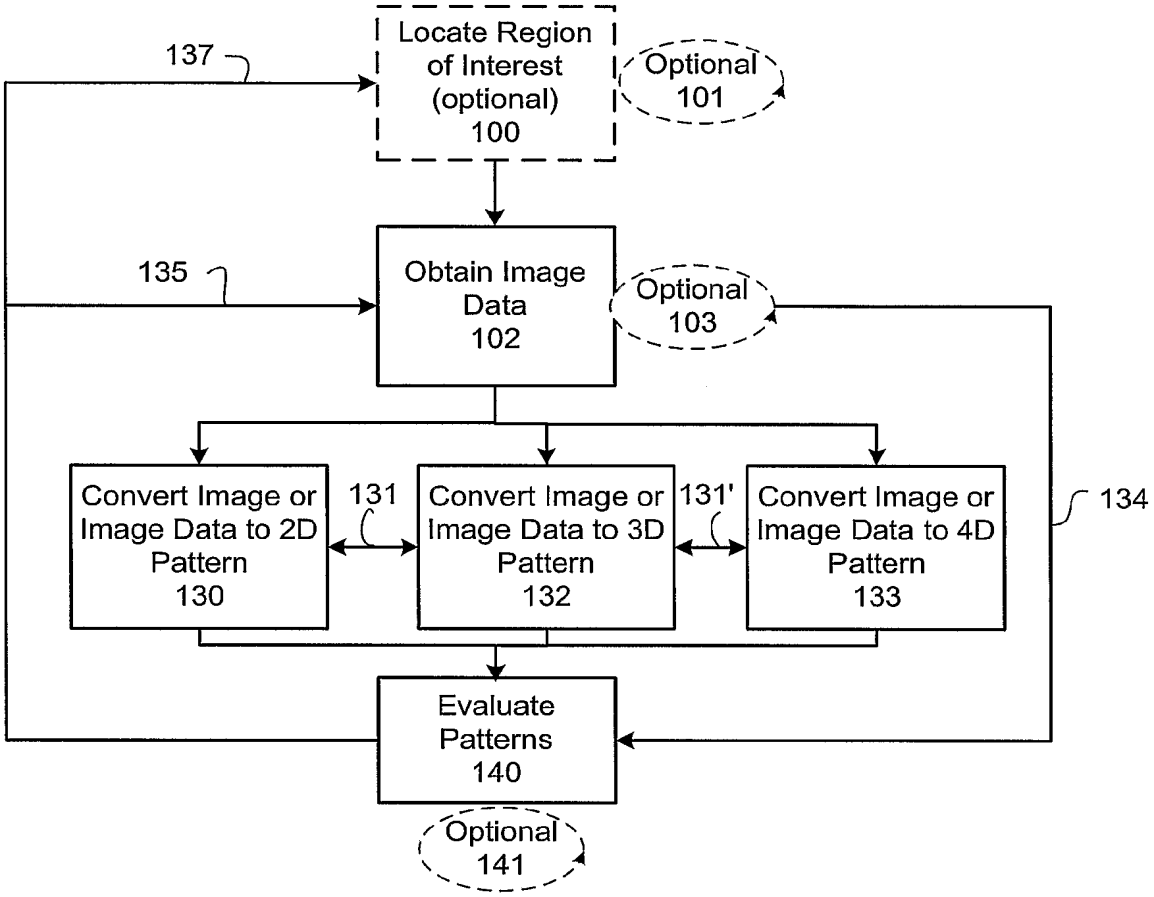

Locate Region of Interest (optional) 100
Optional 101
137
Obtain Image Data 102
Optional 103
135
Convert Image or Image Data to 2D Pattern 130
131
Convert Image or Image Data to 3D Pattern 132
131'
Convert Image or Image Data to 4D Pattern 133
134
Evaluate Patterns 140
Optional 141

FIG. 5A

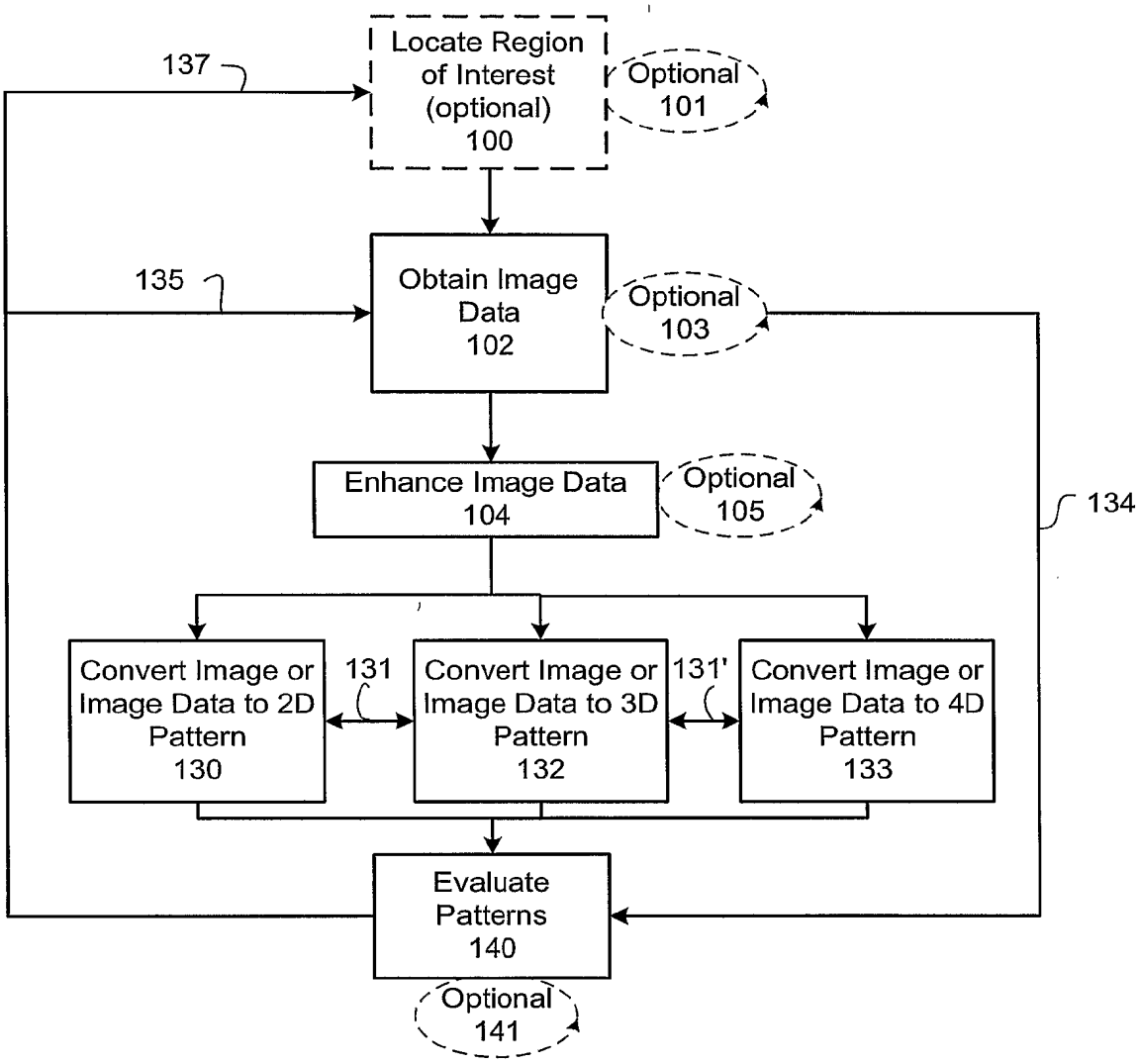

137
Locate Region of Interest (optional) 100
Optional 101
135
Obtain Image Data 102
Optional 103
Enhance Image Data 104
Optional 105
134
Convert Image or Image Data to 2D Pattern 130
131
Convert Image or Image Data to 3D Pattern 132
131'
Convert Image or Image Data to 4D Pattern 133
Evaluate Patterns 140
Optional 141

FIG. 5B

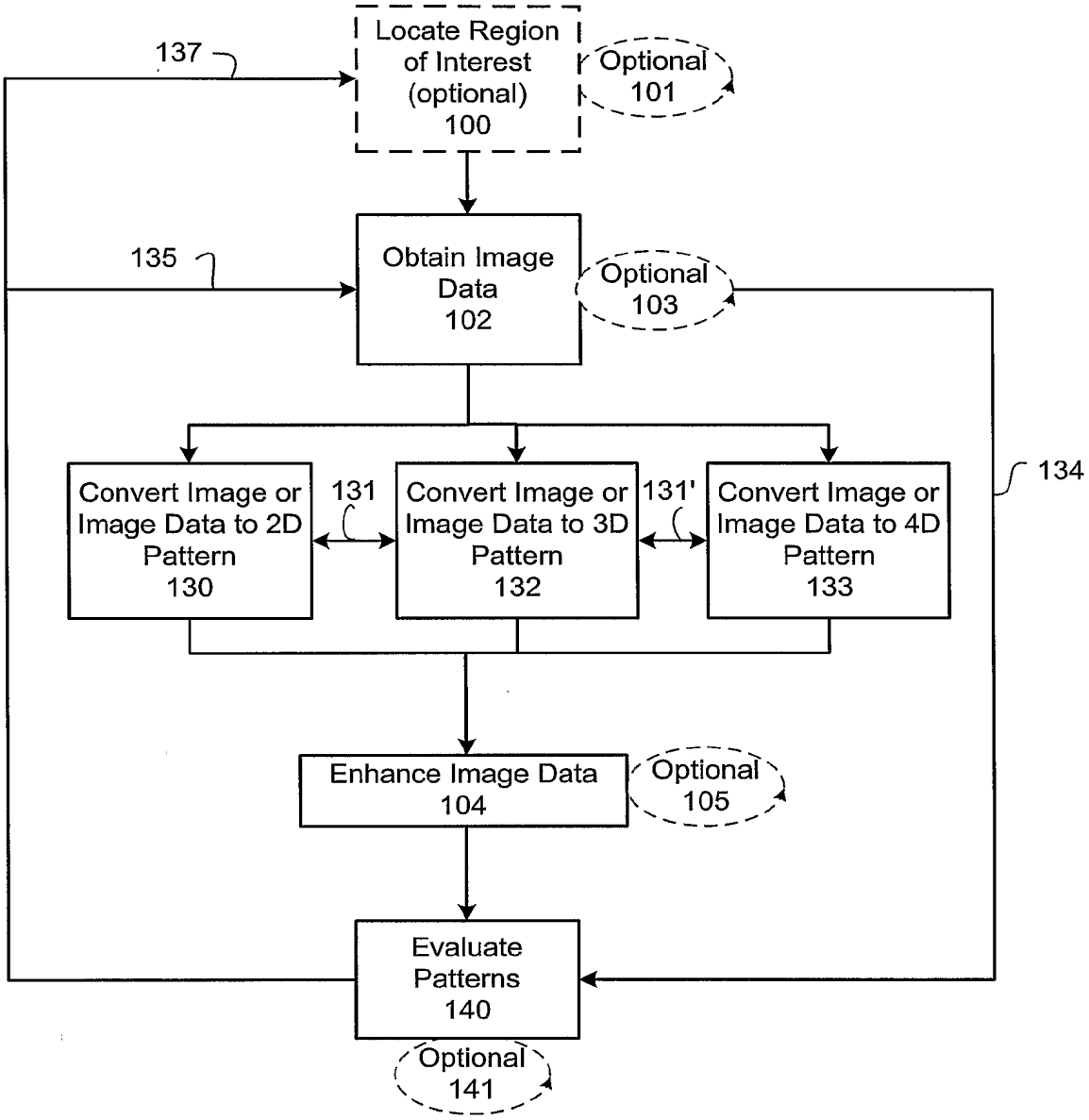

Locate Region of Interest (optional) 100
Optional 101
137
Obtain Image Data 102
Optional 103
135
Convert Image or Image Data to 2D Pattern 130
131
Convert Image or Image Data to 3D Pattern 132
131'
Convert Image or Image Data to 4D Pattern 133
134
Enhance Image Data 104
Optional 105
Evaluate Patterns 140
Optional 141

FIG. 5C

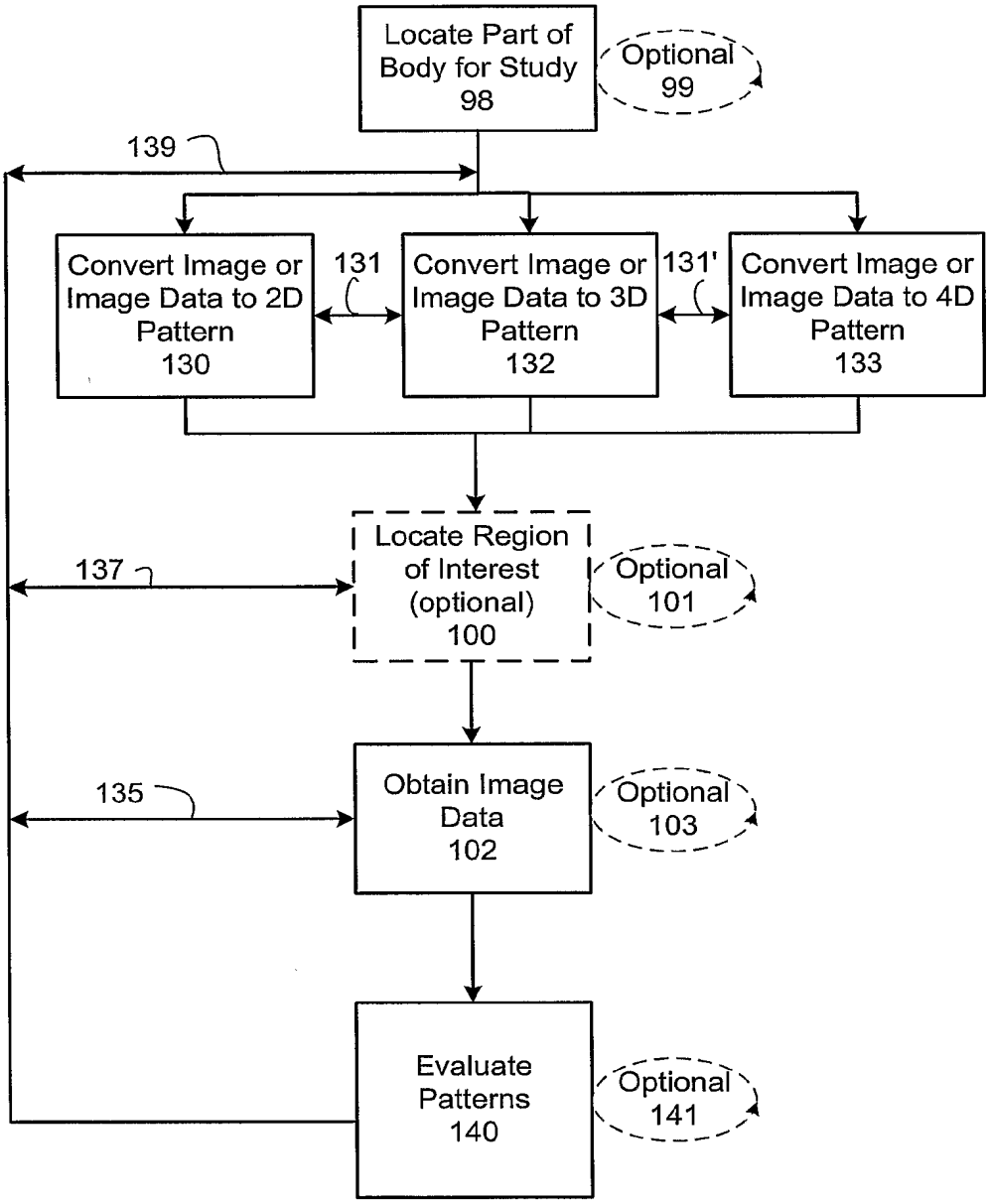

Locate Part of Body for Study 98
Optional 99
139
Convert Image or Image Data to 2D Pattern 130
131
Convert Image or Image Data to 3D Pattern 132
131'
Convert Image or Image Data to 4D Pattern 133
Locate Region of Interest (optional) 100
Optional 101
137
Obtain Image Data 102
Optional 103
135
Evaluate Patterns 140
Optional 141

FIG. 5D

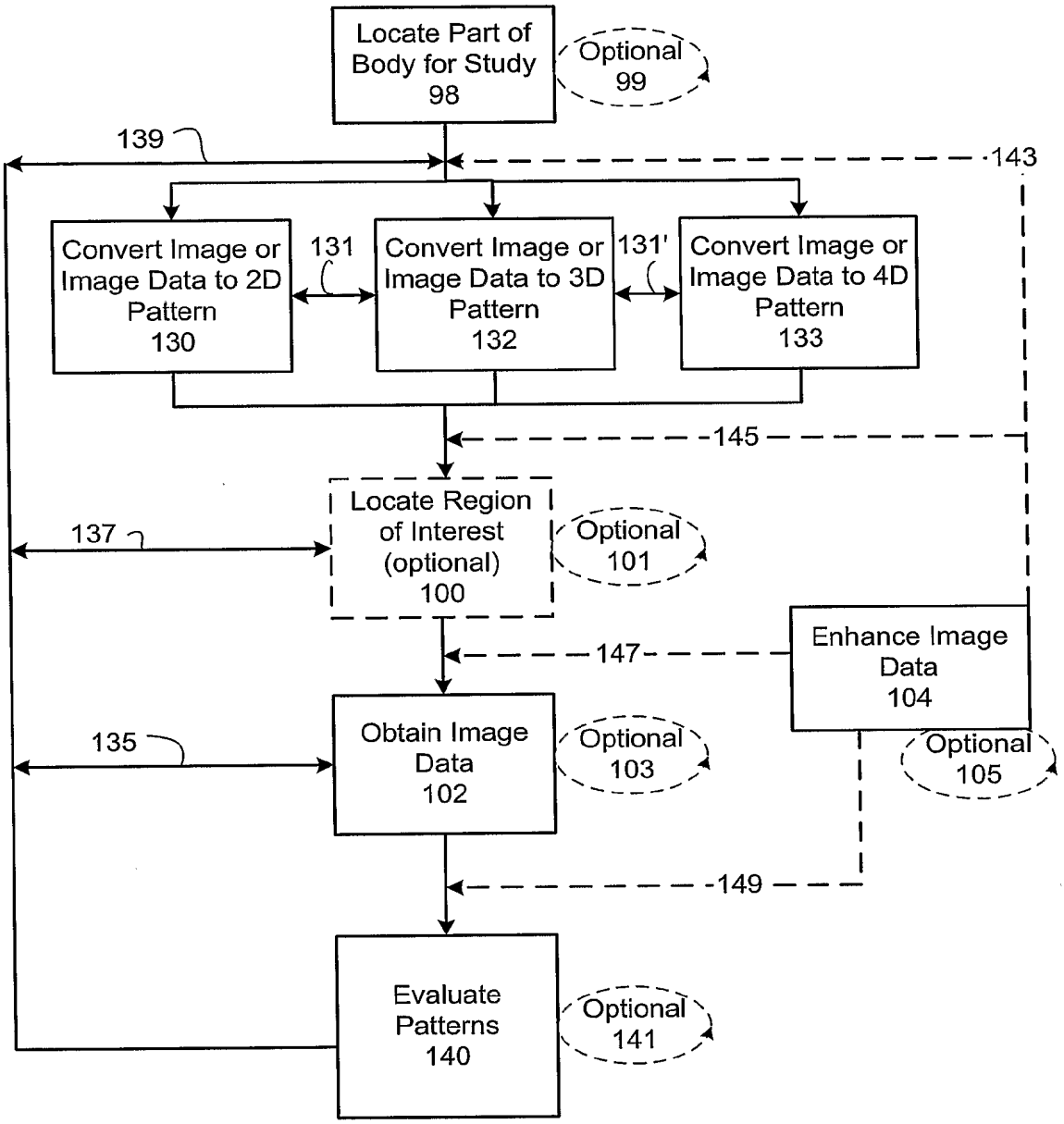

Locate Part of Body for Study 98
Optional 99
139
143
Convert Image or Image Data to 2D Pattern 130
131
Convert Image or Image Data to 3D Pattern 132
131'
Convert Image or Image Data to 4D Pattern 133
145
Locate Region of Interest (optional) 100
Optional 101
137
147
Enhance Image Data 104
Optional 105
Obtain Image Data 102
Optional 103
135
149
Evaluate Patterns 140
Optional 141

FIG. 5E

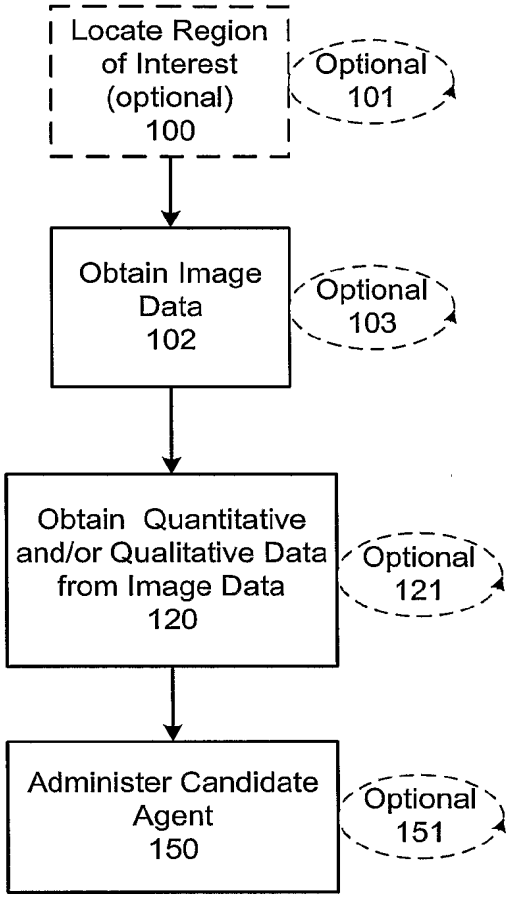

Locate Region of Interest (optional) 100
Optional 101
Obtain Image Data 102
Optional 103
Obtain Quantitative and/or Qualitative Data from Image Data 120
Optional 121
Administer Candidate Agent 150
Optional 151

FIG. 6A

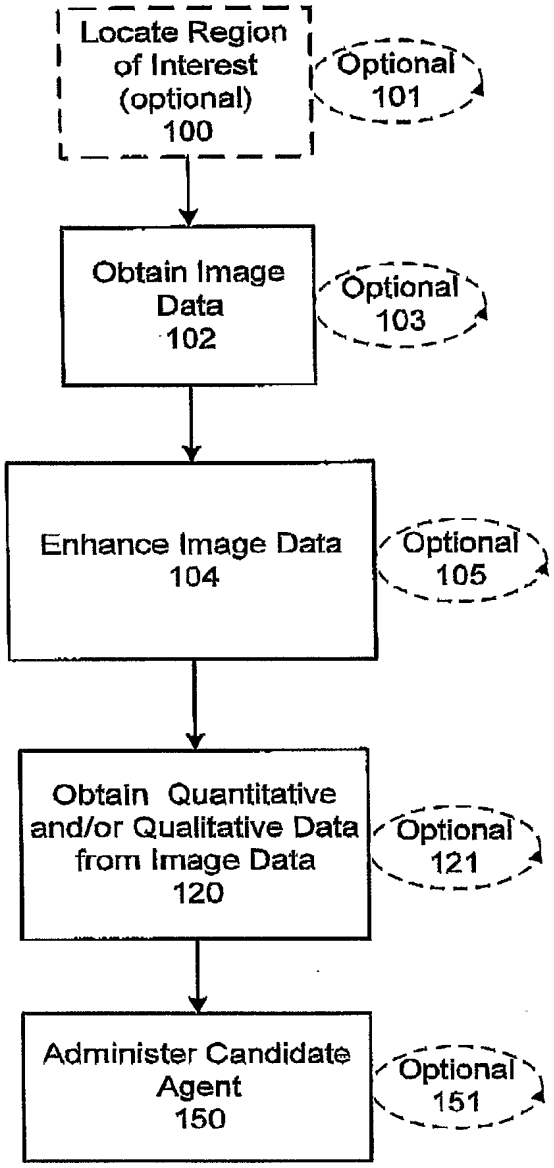

Locate Region of Interest (optional) 100
Optional 101
Obtain Image Data 102
Optional 103
Enhance Image Data 104
Optional 105
Obtain Quantitative and/or Qualitative Data from Image Data 120
Optional 121
Administer Candidate Agent 150
Optional 151

FIG. 6B

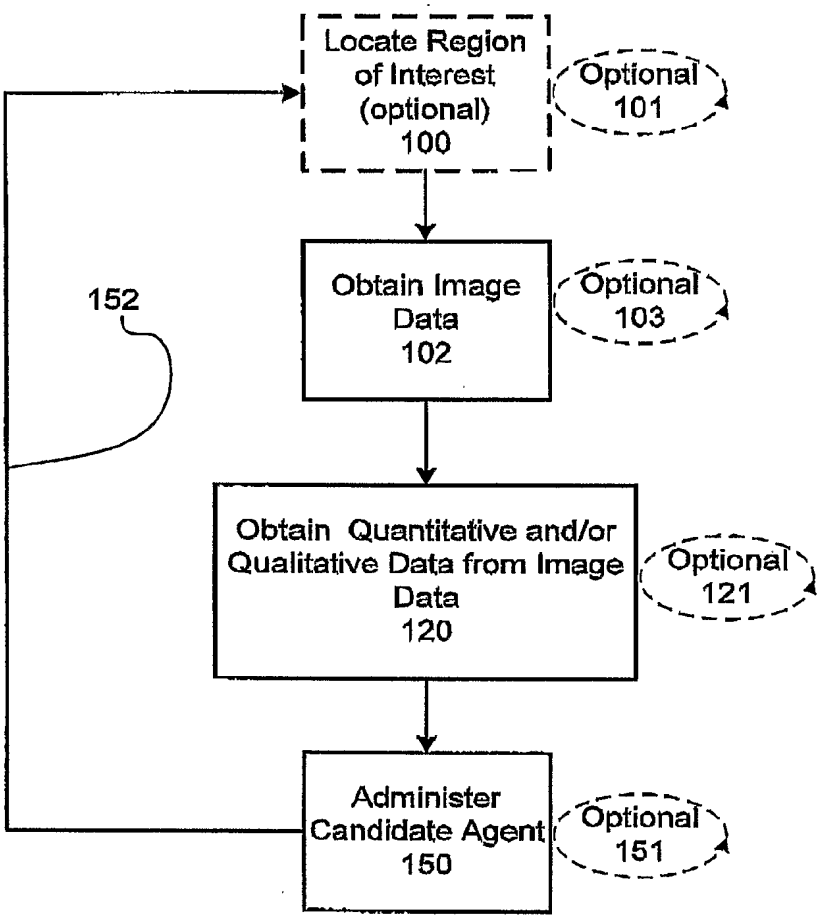

Locate Region of Interest (optional) 100
Optional 101
Obtain Image Data 102
Optional 103
152
Obtain Quantitative and/or Qualitative Data from Image Data 120
Optional 121
Administer Candidate Agent 150
Optional 151

FIG. 6C

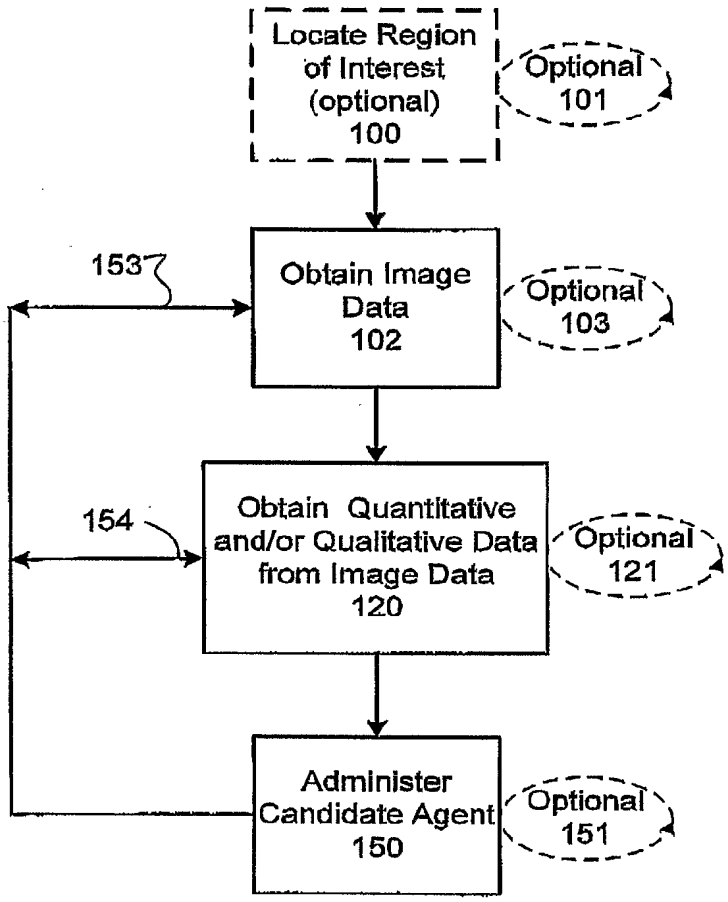

Locate Region of Interest (optional) 100
Optional 101
153
Obtain Image Data 102
Optional 103
154
Obtain Quantitative and/or Qualitative Data from Image Data 120
Optional 121
Administer Candidate Agent 150
Optional 151

FIG. 6D

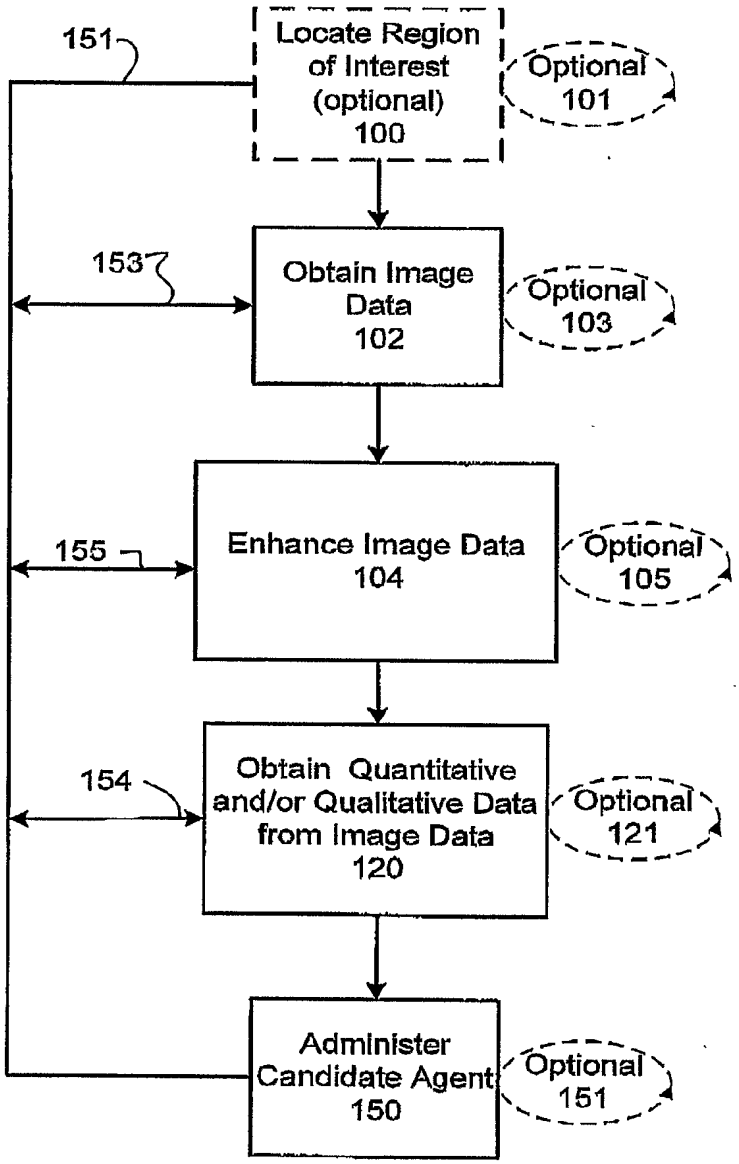

151
Locate Region of Interest (optional) 100
Optional 101
153
Obtain Image Data 102
Optional 103
155
Enhance Image Data 104
Optional 105
154
Obtain Quantitative and/or Qualitative Data from Image Data 120
Optional 121
Administer Candidate Agent 150
Optional 151

FIG. 6E

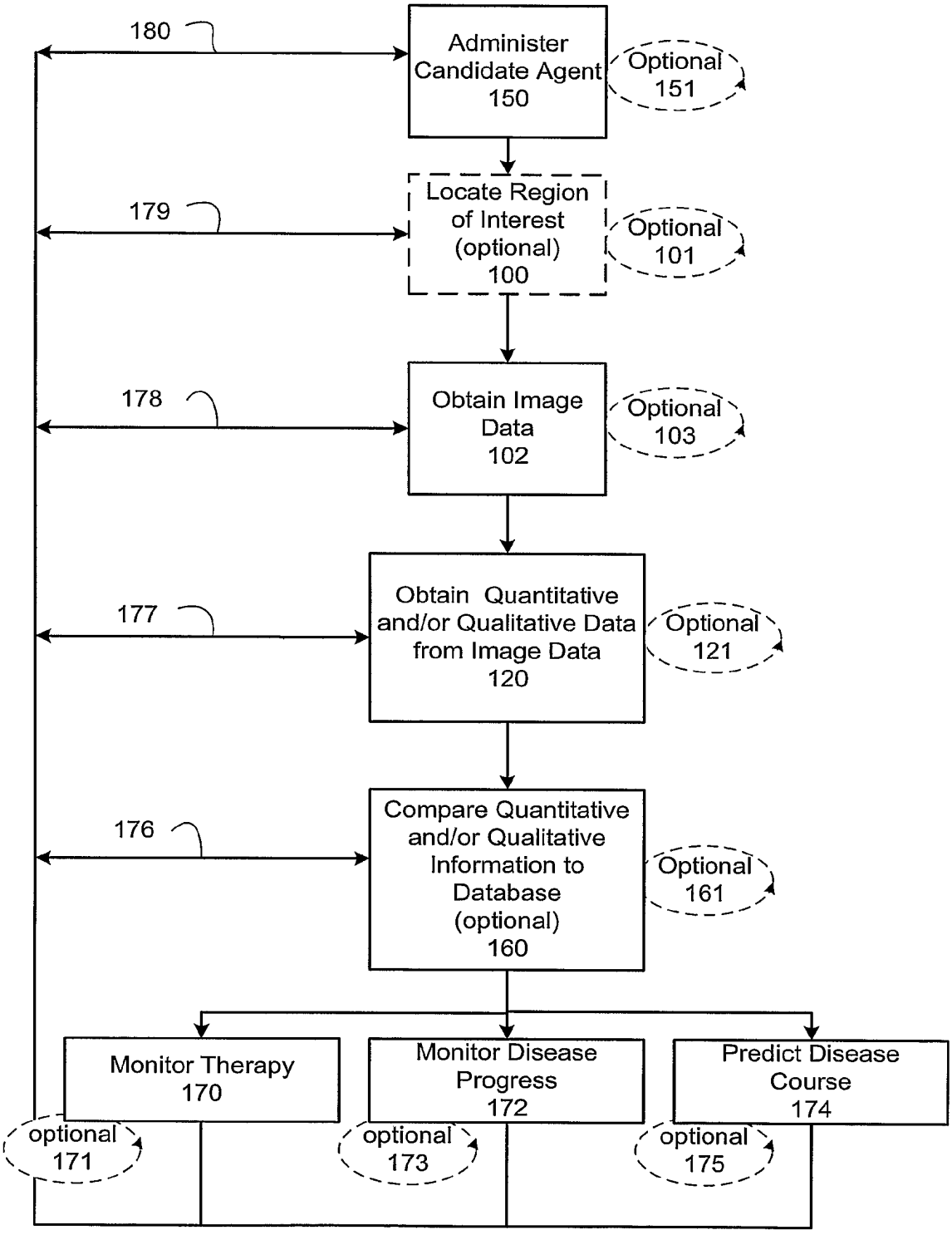

180
Administer Candidate Agent 150
Optional 151
179
Locate Region of Interest (optional) 100
Optional 101
178
Obtain Image Data 102
Optional 103
177
Obtain Quantitative and/or Qualitative Data from Image Data 120
Optional 121
176
Compare Quantitative and/or Qualitative Information to Database (optional) 160
Optional 161
Monitor Therapy 170
optional 171
Monitor Disease Progress 172
optional 173
Predict Disease Course 174
optional 175

FIG. 7A

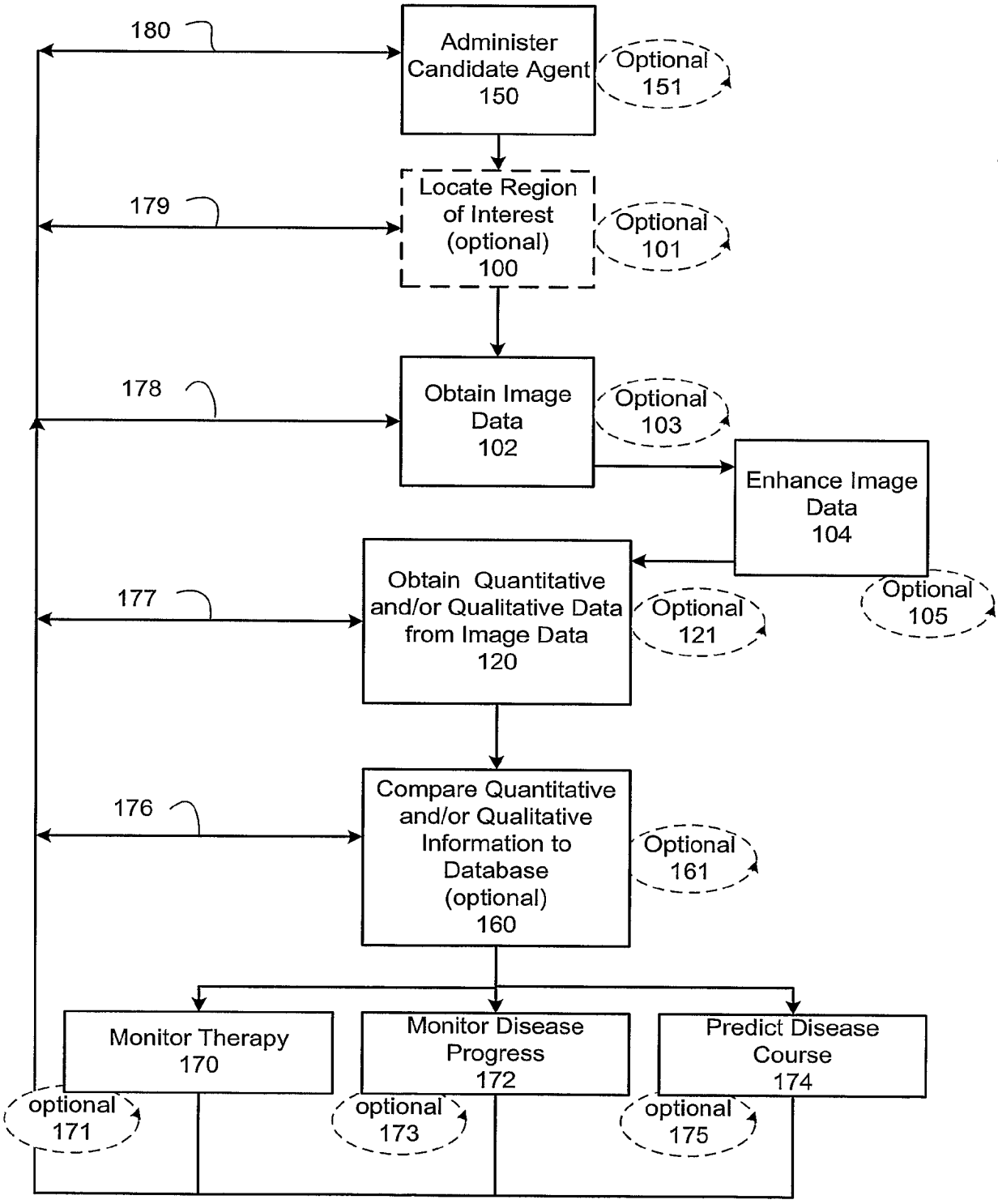

180
Administer Candidate Agent 150
Optional 151
179
Locate Region of Interest (optional) 100
Optional 101
178
Obtain Image Data 102
Optional 103
Enhance Image Data 104
Optional 105
177
Obtain Quantitative and/or Qualitative Data from Image Data 120
Optional 121
176
Compare Quantitative and/or Qualitative Information to Database (optional) 160
Optional 161
Monitor Therapy 170
optional 171
Monitor Disease Progress 172
optional 173
Predict Disease Course 174
optional 175

FIG. 7B

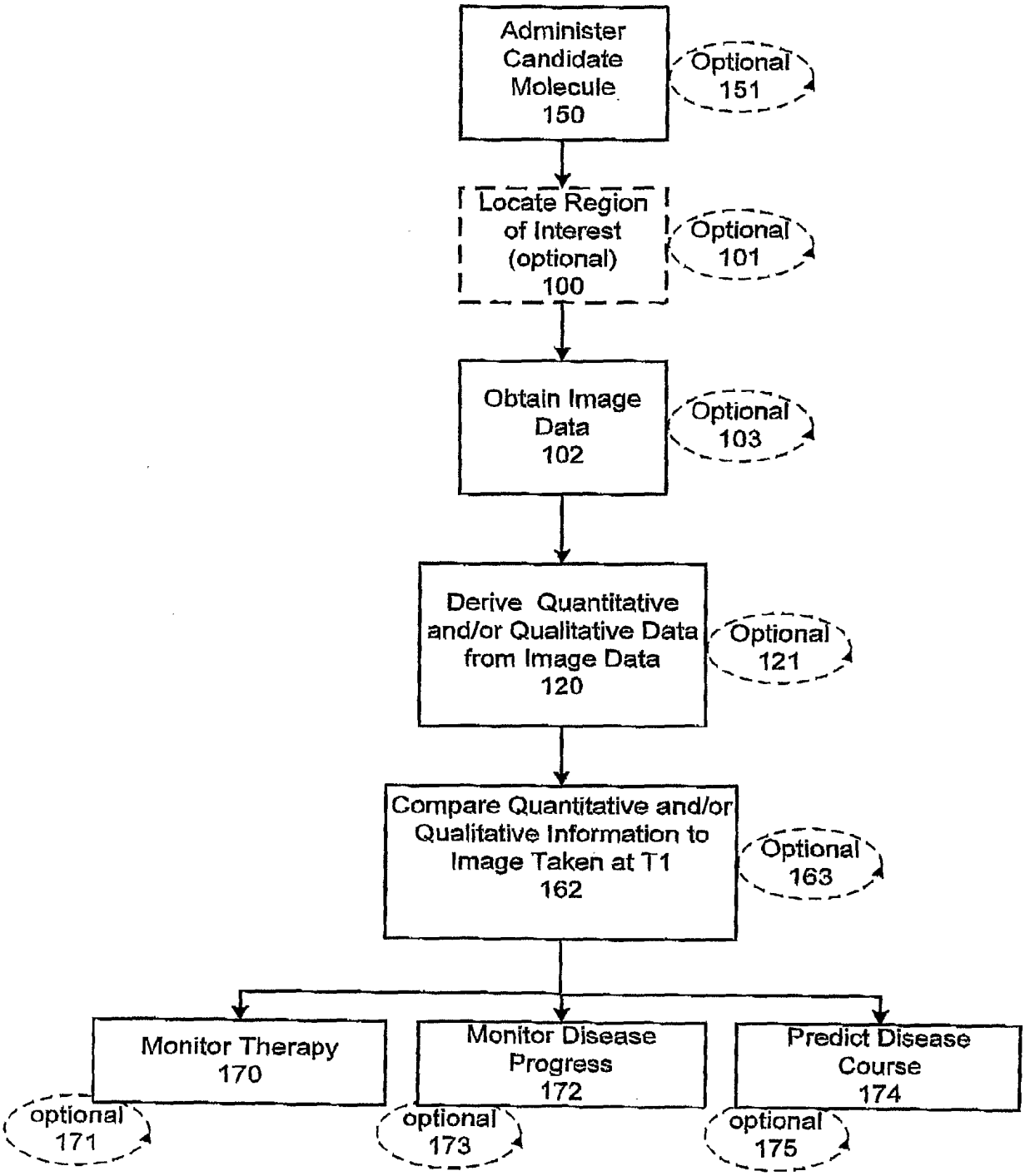

Administer Candidate Molecule 150
Optional 151
Locate Region of Interest (optional) 100
Optional 101
Obtain Image Data 102
Optional 103
Derive Quantitative and/or Qualitative Data from Image Data 120
Optional 121
Compare Quantitative and/or Qualitative Information to Image Taken at T1 162
Optional 163
Monitor Therapy 170
optional 171
Monitor Disease Progress 172
optional 173
Predict Disease Course 174
optional 175

FIG. 7C

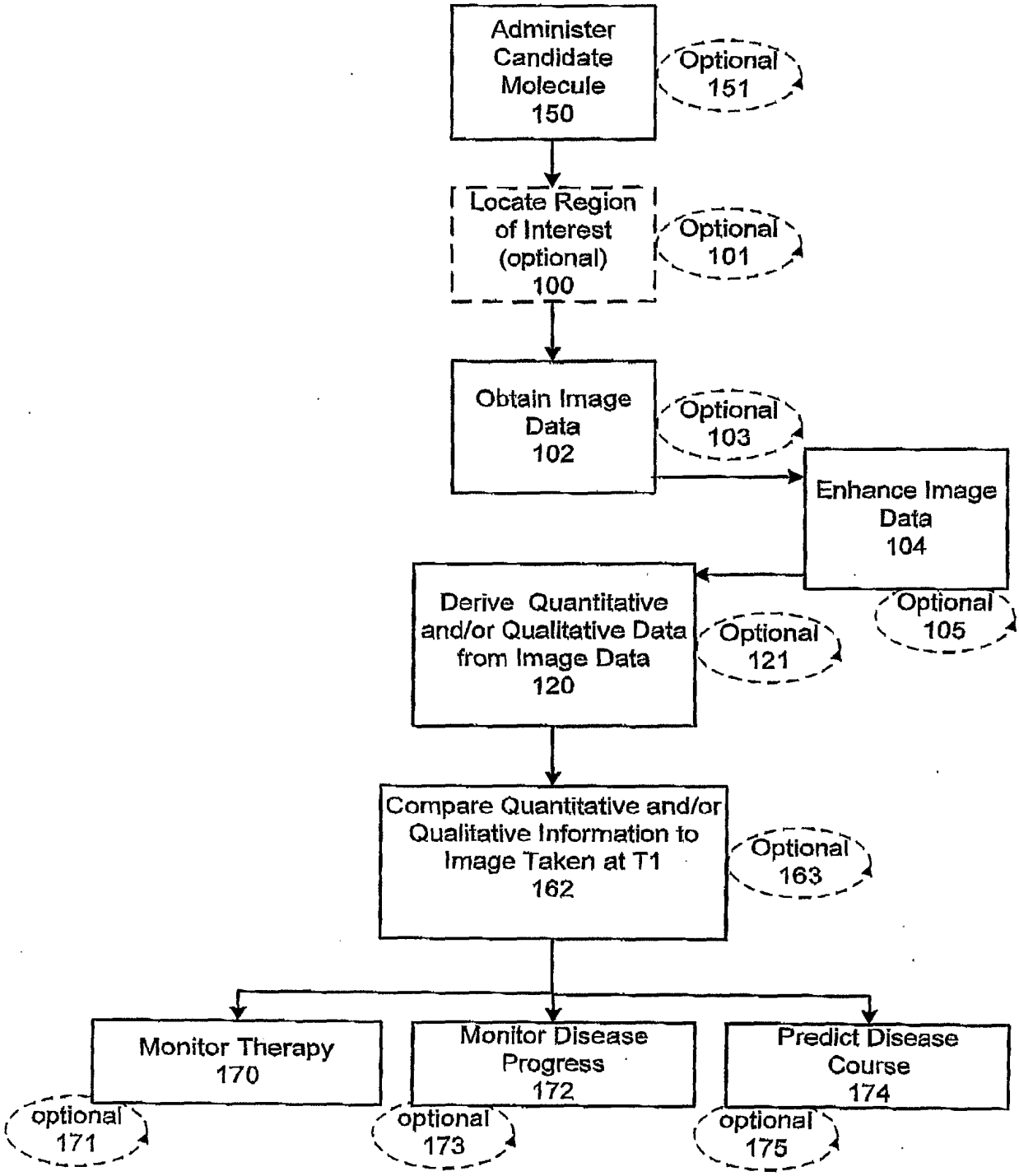

Administer Candidate Molecule 150
Optional 151
Locate Region of Interest (optional) 100
Optional 101
Obtain Image Data 102
Optional 103
Enhance Image Data 104
Optional 105
Derive Quantitative and/or Qualitative Data from Image Data 120
Optional 121
Compare Quantitative and/or Qualitative Information to Image Taken at T1 162
Optional 163
Monitor Therapy 170
optional 171
Monitor Disease Progress 172
optional 173
Predict Disease Course 174
optional 175

FIG. 7D

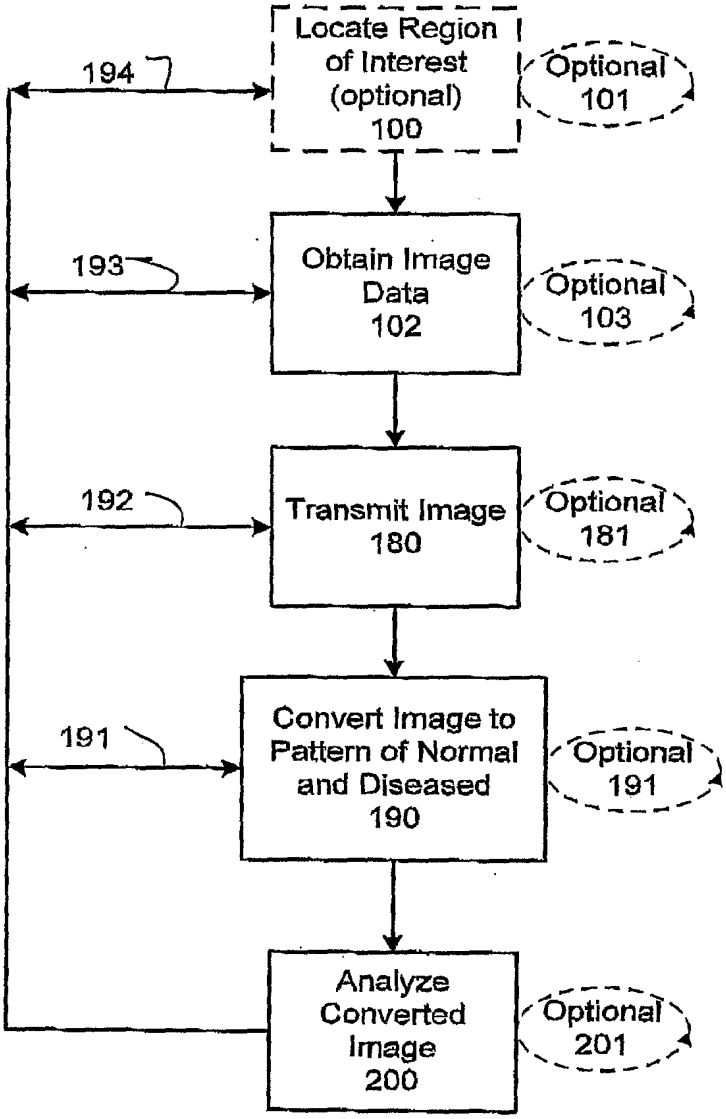

Locate Region of Interest (optional) 100
Optional 101
194
Obtain Image Data 102
Optional 103
193
Transmit Image 180
Optional 181
192
Convert Image to Pattern of Normal and Diseased 190
Optional 191
191
Analyze Converted Image 200
Optional 201

FIG. 8A

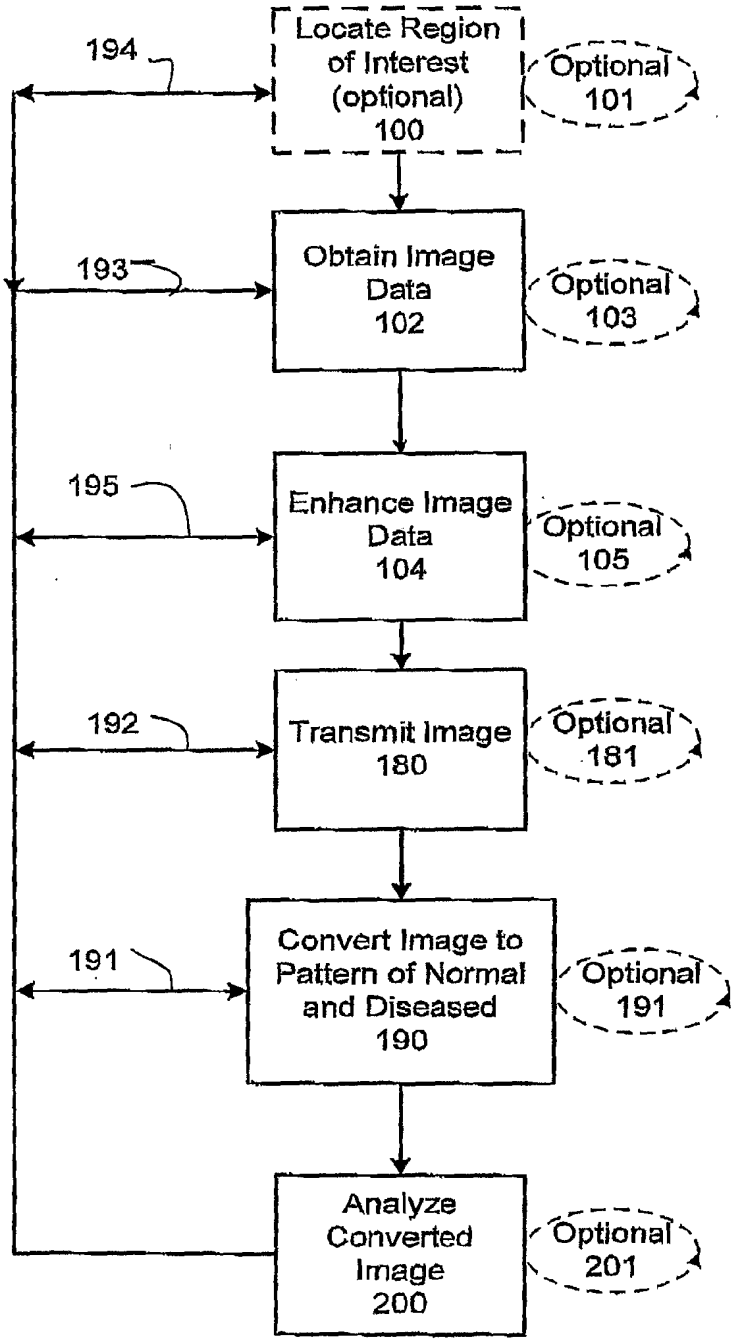

Locate Region of Interest (optional) 100
Optional 101
194
Obtain Image Data 102
Optional 103
193
Enhance Image Data 104
Optional 105
195
Transmit Image 180
Optional 181
192
Convert Image to Pattern of Normal and Diseased 190
Optional 191
191
Analyze Converted Image 200
Optional 201

FIG. 8B

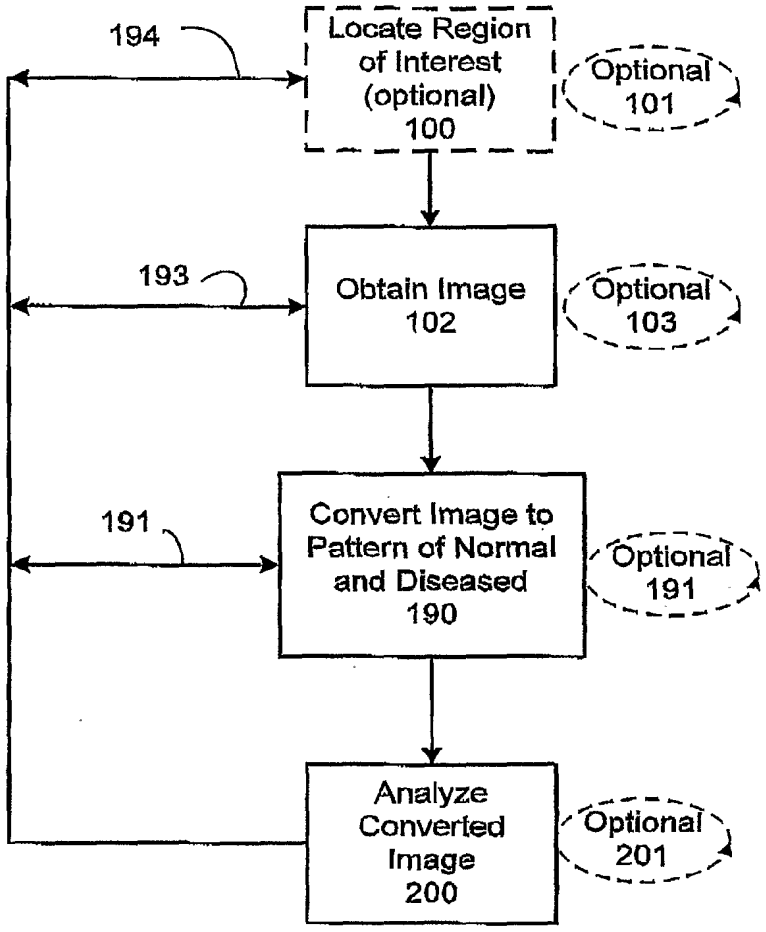

194
Locate Region of Interest (optional) 100
Optional 101
193
Obtain Image 102
Optional 103
191
Convert Image to Pattern of Normal and Diseased 190
Optional 191
Analyze Converted Image 200
Optional 201

FIG. 8C

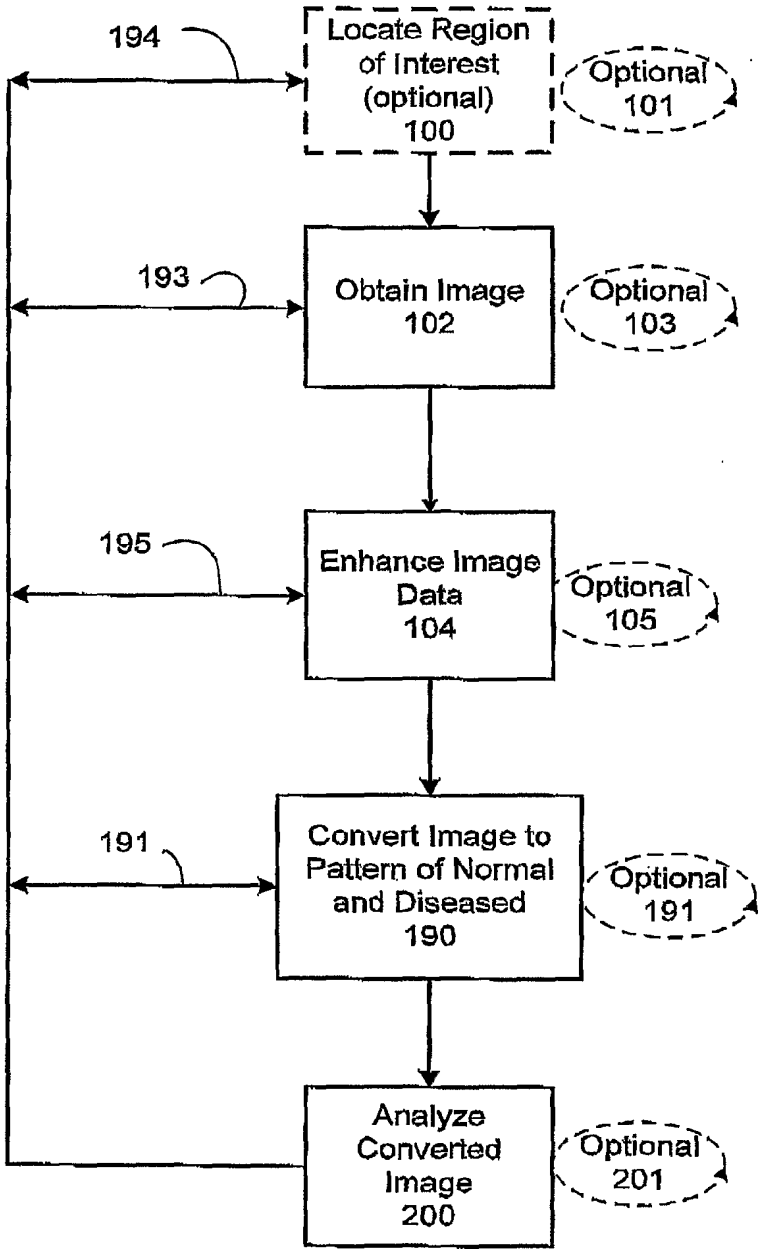

194
Locate Region of Interest (optional) 100
Optional 101
193
Obtain Image 102
Optional 103
195
Enhance Image Data 104
Optional 105
191
Convert Image to Pattern of Normal and Diseased 190
Optional 191
Analyze Converted Image 200
Optional 201

FIG. 8D

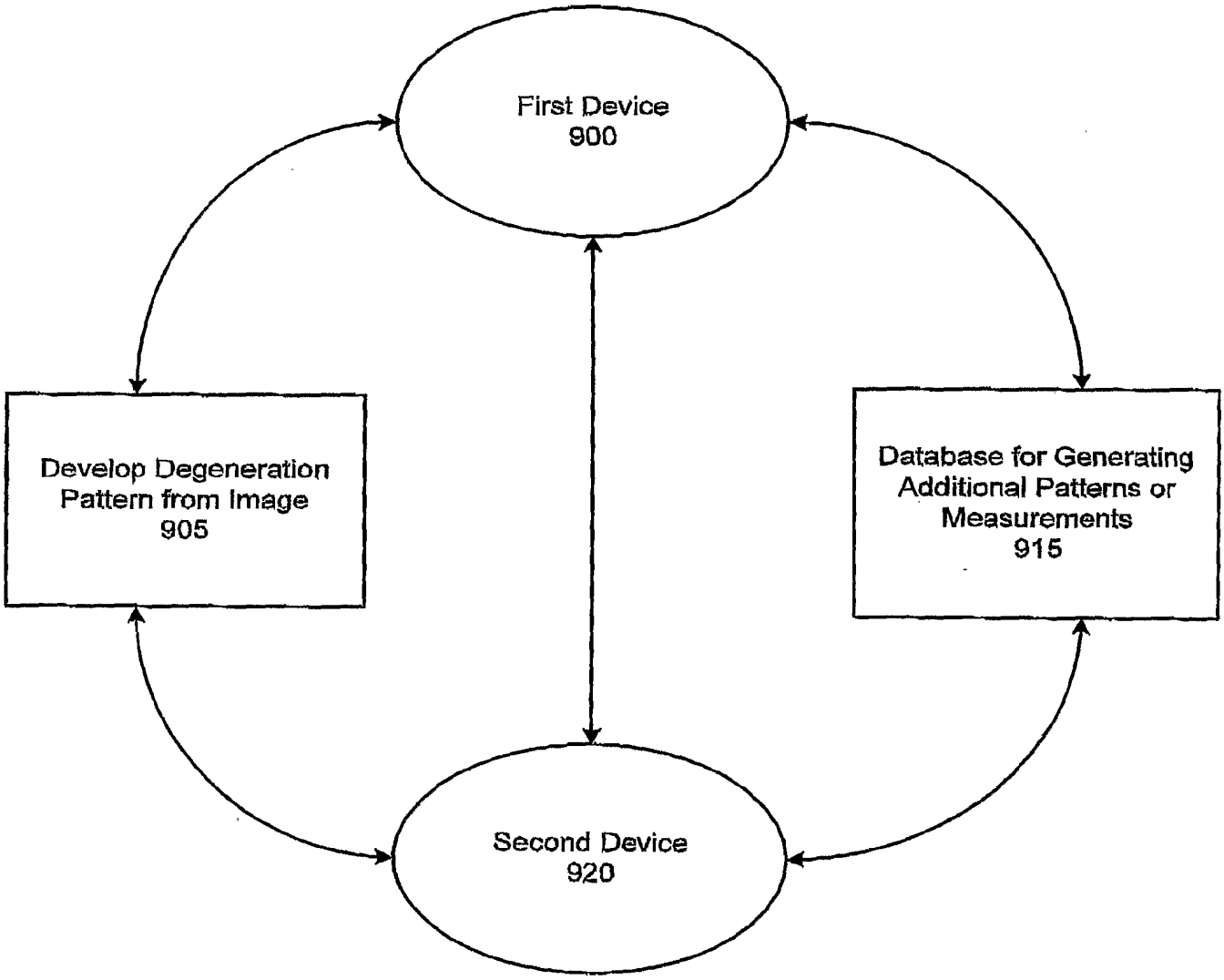

First Device
900
Develop Degeneration Pattern from Image
905
Database for Generating Additional Patterns or Measurements
915
Second Device
920

FIG. 9

INTERNATIONAL SEARCH REPORT

Internat application No
PCT/US 03/30004

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 G06F19/00 A61B6/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 G06F A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 72216 A (JOERGENSEN JAN TROEST ;HYLDSTRUP LARS (DK); ROSHOLM ANDERS (DK); T) 30 November 2000 (2000-11-30) page 5, line 19 -page 16, line 9 ---	7,8
X	WO 02 22014 A (ANDRIACCHI THOMAS P ;UNIV LELAND STANFORD JUNIOR (US); STEINES DAV) 21 March 2002 (2002-03-21) cited in the application the whole document ---	7,8
X	US 5 320 102 A (O'BYRNE ELIZABETH ET AL) 14 June 1994 (1994-06-14) column 2, line 40 -column 11, line 25; claims 1-19 ---	7,8

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 February 2004	25/02/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	BIRKENMAIER, T

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Internat Application No
PCT/US 03/30004

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 673 298 A (MAZESS RICHARD B) 30 September 1997 (1997-09-30) column 3, line 20 -column 25, line 25	7,8
Y	US 4 721 112 A (HIRANO YOSHIO ET AL) 26 January 1988 (1988-01-26) column 1, line 55 -column 9, line 10	7,8

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 03/30004

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 1-6,9-61
because they relate to subject matter not required to be searched by this Authority, namely:

Claims 1, 9-61: Diagnostic method Rule 39.1(iv) PCT; Claims 5, 6: Method for treatment of the body by therapy Rule 39.1(iv) PCT; Claims 2-4: Rule 39.1(vi) PCT - Program for computers Rule 39.1(iv) PCT;

2. [X] Claims Nos.: -
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

The present claims 7 and 8 do not define the subject-matter of the invention in terms of technical features within the meaning of Article 6.3 PCT.
Consequently, the search has been carried out for those parts of the application which appear to be supported and disclosed, namely those parts relating to systems for diagnosing bone diseases, mentioned in the description par. 13, 35, 95.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Interna Application No
PCT/US 03/30004

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 0072216 A	30-11-2000	AU	4744500 A	12-12-2000
		WO	0072216 A1	30-11-2000
		EP	1121661 A1	08-08-2001
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		US	5509042 A	16-04-1996
		US	5291537 A	01-03-1994
		US	5228068 A	13-07-1993
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		AU	5796896 A	30-12-1996
		WO	9639936 A1	19-12-1996
		CA	2200969 A1	30-05-1996
		EP	0793446 A1	10-09-1997
		JP	10509074 T	08-09-1998
		WO	9615719 A1	30-05-1996
		US	6438201 B1	20-08-2002
		US	5745544 A	28-04-1998
		US	6038281 A	14-03-2000
		US	5533084 A	02-07-1996
		US	5841833 A	24-11-1998
		US	5841832 A	24-11-1998
		WO	9406351 A1	31-03-1994
		US	6160866 A	12-12-2000
		AU	667127 B2	07-03-1996
		AU	4854593 A	12-04-1994
		CA	2123432 A1	31-03-1994
		DE	69325790 D1	02-09-1999
		DE	69325790 T2	30-12-1999
		EP	0611290 A1	24-08-1994
		EP	0783869 A1	16-07-1997
		JP	2719444 B2	25-02-1998
		JP	6511184 T	15-12-1994
		US	5305368 A	19-04-1994
		US	6081582 A	27-06-2000
		US	RE36162 E	23-03-1999
		US	5287546 A	15-02-1994
		US	5480439 A	02-01-1996
		EP	0755219 A1	29-01-1997
		WO	9625086 A1	22-08-1996
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		JP	3031061 B	02-05-1991
		JP	61109557 A	28-05-1986
		EP	0180482 A2	07-05-1986